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A STUDY OF POST-ISCHÆMIC PARÆSTHESIÆ

BY

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Paræsthesiæ of the kind commonly known as "pins and needles" occur spontaneously in a variety of conditions. They may be produced deliberately by mechanical or electrical stimulation of a nerve, by overbreathing, or by cutting off the circulation to a limb and then releasing it. The present study is mainly concerned with the paræsthesiæ which follow a period of circulatory arrest in a limb, and its object has been to differentiate the various types of sensation which occur in these circumstances, determining their site of origin and their peripheral and central nervous pathways.

Historical

Several authors have described the sensory phenomena which occur during and after compression of a nerve or a limb. Only recent writers made these paræsthesiæ the main subject of their study; in earlier work the sensations were noted during the course of investigations on other problems of human physiology. Goldscheider (1886), while investigating temperature sense, noticed the paræsthesiæ which followed the release of local pressure on nerve trunks. He described these paræsthesiæ carefully, and they appear to be similar to those following release of the circulation to a limb. Ebbecke (1922) made detailed studies of the sensations resulting from electrical stimulation of nerves. He also wrote of the paræsthesiæ ("Nervenschwirren") produced by other methods, including those felt during recovery from pressure paralysis, and at the onset of anæsthesia caused by the intraneural injection of a local anæsthetic; he was clearly of the opinion that all these forms of paræsthesiæ were alike. Bourguignon and Laugier (1923), in studies of chronaxie, described two forms of paræsthesiæ, those occurring during a period of circulatory arrest in a limb, and those occurring after release of the circulation. Again, Lewis and Grant (1925), while investigating reactive hyperæmia, noted that intense tingling and sometimes painful cramp occurred soon after restoration of the circulation to an ischæmic limb. Reid (1931), during experiments on muscular reactions following ischæmia of a limb, noted the sensations which occurred at the same time. He was of the opinion that they were caused by the restoration of circulation and arose in the sensory end-organs. Bazett and McGlone (1929, 1932), having extensively investigated the thermal sensations which follow release of the circulation, concluded that they were true paræsthesiæ originating in the appropriate end-organs rather than in the nerve trunks. In their studies they made observations on the "tingling" and "cramp" sensations which they at first believed arose from the end-organs; later, they expressed agreement with the following views of Lewis, Pickering, and Rothschild (1931). These authors investigated ischæmic paralysis and anæsthesia. In the account of their studies, they included a note on the sensations which followed release of the circulation to a limb. They recognized two components to the sensation, "tingling" or "pricks," and "pseudo-cramp." They presented evidence to show that the nerve impulses responsible for the sensations arose in the segments of nerves actually compressed by the occluding cuff; they believed that it was the nerve fibres subserving the sense of touch which were concerned in the production of the tingling sensation, and that the nerves from muscle afferent end-organs were concerned in the production of "pseudo-cramp."

Zotterman (1933), in a study of sensory disturbances resulting from ischæmia, confirmed many of the findings of Lewis, Pickering, and Rothschild. Like them, he showed that these sensations arose in the proximal parts of the nerve trunks, but he thought, from the painful character of the sensations,

that they were an affair of pain-conducting fibres rather than those of touch. While studying accommodation in human nerves, Kugelberg (1944) included observations on two forms of paræsthesiæ occurring during and after the arrest of bloodflow to a limb. He related their appearance to concurrent changes in nerve excitability. The paræsthesiæ which occurred during ischæmia he called " tactile paræsthesia." The paræsthesia which followed release of the circulation he thought consisted of two components, both painful in character; the first, an " irradiating stinging sensation," he considered was conducted by fibres subserving pain sense, while the second, consisting of " innumerable well-localized short pricks," was of an uncertain nature but was conducted in fibres finer than those transmitting light touch. He based these conclusions largely on comparisons with similar, though not identical, sensations which resulted from the stimulation of nerves by other methods, notably by various forms of electrical current. Kugelberg also investigated the feeling of tension which followed release of the circulation, and its relation to the paræsthesiæ and the spasms found in tetany. More recently, Weddell and Sinclair (1947) investigated " compression tingling " and " release pricking," the sensory phenomena occurring, respectively, during and after the arrest of the circulation to a limb. They deduced that " compression tingling " arose as a result of changes in the nerves compressed by the occluding cuff. They considered, however, that " release pricking " resulted from the stimulation of pain nerve-endings by metabolites during their removal from the tissues on return of the circulation.

From a study of the literature it is clear that the sensation which follows release of the circulation is considered by many authors to consist of more than one component. It is also apparent that there is a lack of uniform terminology: words like " tingling " are used to describe differing sensations by different authors, and this makes comparison of their results difficult. Little more is to be gained by what Zotterman calls " introspective analysis " of these paræsthesiæ. It would seem to be difficult to draw conclusions concerning the nature and mechanism of various kinds of paræsthesiæ which feel subjectively the same, but which occur under differing circumstances or are induced in different ways; it becomes even more difficult to do so when the sensation is complex, and when one component of it can be separated from the others only by a mental effort.

Definitions

It is possible to induce the individual components of the paræsthesiæ separately by means of various measures to be described later. Having become familiar with these components in their isolated form, it is easy to recognize each of them in experiments in which they occur together.

The following definitions will be used in this study.

Ischæmic paræsthesiæ are those felt during the arrest of the circulation to a limb. Their most noticeable component is a soft, diffuse tingling, felt peripherally. This paræsthesia is transient, lasting only a few minutes however long the ischæmia lasts. It disappears on rubbing the skin in the area where it is felt, and it invariably goes immediately the circulation is restored.

Post-ischæmic paræsthesiæ are those which follow release of the circulation to a limb. They consist of at least four components: (1) thermal paræsthesiæ; (2) buzzing or tingling; (3) pricking; (4) pseudo-cramp or a feeling of tension.

With the exception of the thermal paræsthesiæ, all these sensations are felt peripherally. They appear fairly abruptly, allowing their time of onset to be stated to within a few seconds; their termination is less definite, for they fade gradually.

1. Thermal paræsthesiæ are the first to be felt on return of the circulation. They consist of changing sensations of warmth and cold, and often of indefinable feelings which may only be expressed as " temperature " of some kind. These paræsthesiæ have been studied extensively by Bazett and McGlone, and will be given no further consideration in this paper.

2. Buzzing or tingling is in most subjects the next sensation to be felt. It is often described by subjects as a vibrating sensation and is localized superficially. When it is at its height it may be momentarily increased by any stimulus which deforms the skin in the area where it is felt, but not by very light touches. Similar stimuli may also induce this sensation a few seconds before it is due to begin spontaneously. Some minutes later, when the buzzing or tingling is waning, the application of the same stimuli will cause it to disappear, at least temporarily.

3. Pricking, in many subjects, is the most easily induced of the post-ischæmic paræsthesiæ, since it may follow periods of ischæmia too brief to produce tingling or pseudo-cramp. When present with the other paræsthesiæ, it is usually the most noticeable sensation. It consists of a feeling of rapidly repeated, irregularly spaced, discrete, little pricks, less sharp and painful than the pinpricks employed in the clinical testing of sensation; they are felt superficially, in the skin. This paræsthesia, when

at its height, may be increased momentarily by firm pressure or by gross movements in the area where it is felt; such stimuli will also produce pricking some seconds before it is due to begin spontaneously.

4. Pseudo-cramp is the name given by Lewis, Pickering, and Rothschild to a feeling of tension felt in the hand, wrist, and forearm in experiments on the upper limb, or in the foot and calf in experiments on the lower limb. It is a sensation which gives the impression that the fingers and wrist are being strongly flexed. Active and passive movements of the fingers and wrist increase this sensation, which is felt only after prolonged periods of circulatory arrest. After even longer periods of ischæmia, this paræsthesia is followed by involuntary muscular contraction which actually produces flexion of the fingers and wrist.

The following typical experiment illustrates the order in which the paræsthesiæ appear, their mode of onset, and the time for which they may be expected to last.

Experiment 1.—A sphygmomanometer cuff 12 cm. wide was placed on the arm above the elbow. The arm was elevated to prevent venous congestion, and the pressure in the cuff quickly raised to 200 mm. of mercury and maintained at this level, which was above the systolic blood pressure. With the arm rested on a table, the following events were observed.

About two minutes after arrest of the circulation, a soft tingling sensation (ischæmic paræsthesia) was felt, beginning in the finger-tips and spreading to the palm and then to the wrist. This sensation increased slightly in intensity, reached its maximum in a minute, and then subsided, so that about five minutes after the onset of occlusion it was gone.

For the remainder of the period of circulatory arrest, no further paræsthesiæ were felt. Ischæmic paralysis and anæsthesia began to be obvious after fifteen minutes.

After thirty minutes the pressure in the cuff was released; the sensations which followed were the post-ischæmic paræsthesiæ. Two to three seconds after release, thermal paræsthesiæ were felt in the whole limb, although they were more marked in the hand. They continued for about forty seconds. During this time both anæsthesia and paralysis recovered completely. About fifty seconds after release, the first striking sensation was felt; it consisted of tingling in the fingers and palms. It rapidly increased in intensity and spread to the whole hand and wrist. At the same time the feeling of tension developed. About seventy seconds after release, at a time when the tingling and pseudo-cramp were still increasing, pricking was felt. Like tingling, it was felt first in the fingers, particularly on their palmar aspects, and spread rapidly to the whole hand and wrist. Two minutes after release of the cuff the total result was a severe and complex combination of sensations. The paræsthesiæ continued strongly until about four minutes after release, by which time it was apparent that the feeling of tension had gone and that pricking had diminished. There remained a continuous tingling with an occasional pricking sensation. This gradually diminished, and finally stopped about fifteen minutes after release of the cuff.

The duration of the post-ischæmic paræsthesiæ in this experiment are represented in Fig. 1. The paræsthesiæ can be appreciated in this clear manner only after the subject has experienced them separately; experience plays a part in the ability to distinguish the various components of the combined sensation. The methods of separating the various components will be described later.

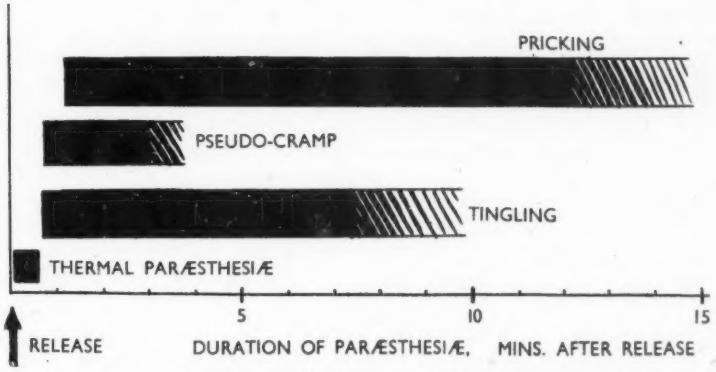


FIG. 1.—Diagram of the onset and duration of paræsthesiæ following arrest of the circulation for thirty minutes with a cuff above the elbow.

This experiment produces slightly different results in different individuals. The precise times of onset of the paræsthesiæ, their duration, and their relative intensity differ from subject to subject, although these factors remain fairly constant over a period of several years in a given subject.

Factors which Modify Post-ischæmic Paræsthesiæ

By altering the procedure given in Experiment 1, differences in the resulting sensations may be observed. The results so obtained will serve as evidence for conclusions relating to the differentiation, the site of origin, and conduction of the paræsthesiæ. An account, here, of the main factors producing these modified results will illustrate certain general characteristics of the paræsthesiæ.

The duration for which the limb is rendered ischæmic is the most important factor in determining the character, distribution, and duration of the paræsthesiæ. Subject to individual variations, it has been found that about five minutes is the minimum period of ischæmia in the arm to be followed by paræsthesiæ. The longer the occlusion, the more severe and more prolonged are the resulting sensations. After short occlusions, tingling and pricking are the only paræsthesiæ experienced, and they are restricted to the fingers and hand; after longer periods the area involved spreads to include the wrist and then the forearm. At least twenty minutes of ischæmia is required for pseudo-cramp to be felt. Whatever the period of ischæmia, there is always a delay of at least fifty seconds following release before the paræsthesiæ, other than thermal, are felt. Fig. 2 illustrates the duration of the paræsthesiæ after different periods of ischæmia; the figures recorded are the averages of many observations made in one subject over the course of two years. In our experiments, duration is selected as being the most easily measured property of paræsthesiæ. Any assessment of intensity in different experiments is too difficult to be of value, although, as a general rule, the more intense the paræsthesiæ, the longer do they last. Observations on intensity may be of value when events occurring simultaneously in the two hands are being compared. The area in which tingling and pricking are felt can usually be mapped out without difficulty. It covers the palmar surfaces of the hand and digits in the upper limb, or the plantar surface of the foot in the lower limb after any period of ischæmia lasting less than twenty minutes; after longer periods of ischæmia the paræsthesiæ may be felt in and proximal to the wrist or ankle, but the area involved is not directly proportional to the duration of ischæmia. Occlusions of five and of twenty minutes' duration cause paræsthesiæ felt in exactly the same area; the only difference is one of intensity.

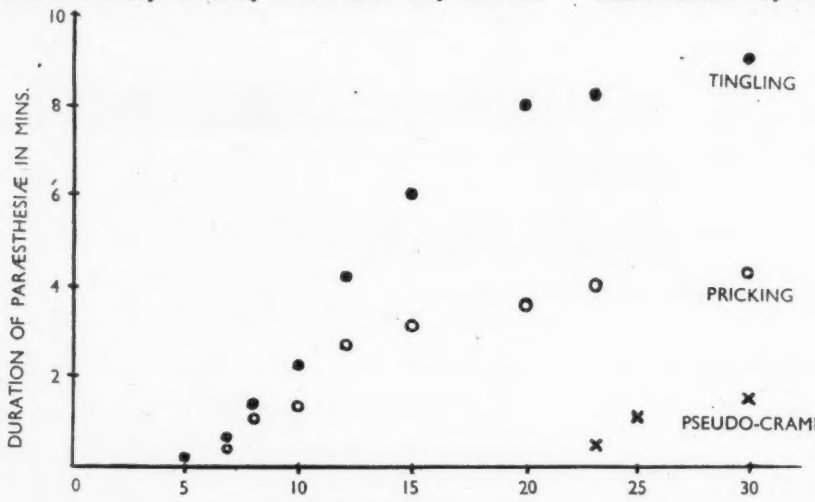


FIG. 2.—Graph showing the duration of paræsthesiæ following various periods of ischæmia. Single cuff above the elbow. (P.W.N.)

In the experiment previously described the circulation in the arm was allowed to continue unimpeded after release of the cuff. If the returned circulation is cut short by re-inflating the cuff the paræsthesiæ are reduced or even suppressed altogether, as the following experiment shows.

Experiment 2. (W.R.M.).—Both arms were rendered ischæmic by inflating cuffs placed above the elbows; after eight minutes the pressure in the cuffs was released. In the right arm the circulation was again arrested after fifteen seconds; the sensations felt in the two hands were then compared. In the left hand paræsthesiæ (tingling and pricking) began one minute after release and continued for four minutes. In the right hand no paræsthesiæ were felt at all, except thermal paræsthesiæ.

It appears that the return of normal circulation for fifteen seconds is insufficient to produce paræsthesiæ. It is to be noted, however, that it is sufficient for some blood to reach the ischæmic tissues of the limb, as the following three facts show. First, reactive hyperæmia appears in the usual way and is obvious five seconds after release; secondly, thermal paræsthesiæ (which originate in peripheral end-organs) are felt after two seconds; and thirdly, ischæmic muscle pain, which may be induced by voluntary contraction just before release of the circulation, vanishes three seconds after release.

If, in Experiment 2, the circulation of the right arm is re-arrested after thirty seconds, then paræsthesiæ are felt, and begin, as in the left hand, one minute after release. Their duration, however, is rather shorter than in the left hand. As the circulation remains arrested throughout the whole time for which these paræsthesiæ are felt, the changes responsible for their production must therefore have been initiated during the thirty seconds of restored

circulation. A certain minimum period of normal circulation following ischæmia is accordingly necessary for the appearance of post-ischæmic paræsthesiæ.

It has been found that, if constant results are to be obtained, at least twenty-four hours must elapse between experiments on the same limb. This applies to all experiments in which the ischæmia lasts more than twenty minutes; it is likely that shorter experiments may safely be repeated at shorter intervals. Perhaps the most noticeable change in the results of an experiment repeated after an hour is a diminution or even an absence of the ischæmic paræsthesia. But post-ischæmic paræsthesiæ are also modified, especially after repeated periods of ischæmia; the pricking element is diminished, the times of onset of the various paræsthesiæ are delayed, and their total duration is reduced.

The position of the occluding cuff determines the amount of a limb which is rendered ischæmic, and which, on release of the cuff, recovers from ischæmia. The more proximally the cuff is placed, the more readily are all forms of post-ischæmic paræsthesiæ produced, for they occur after shorter periods of occlusion, are greater in intensity, and last longer.

The width of the occluding cuff is of no importance provided that the blood flow to the limb is completely arrested. When two adjacent cuffs (total width 24 cm.) are used together to produce ischæmia, and released together, the resulting paræsthesiæ are precisely the same as when only one cuff (12 cm. wide) is used at the same level. By altering the position of the distal cuff, while keeping the proximal cuff in the same position, release of the proximal cuff alone will restore the circulation to various lengths of limb. It will then be found that the longer the length of limb recovering from ischæmia, the more marked will be the paræsthesiæ. When the proximal cuff is placed on the limb so that it overlaps the distal cuff, the recovery of the short segment of limb from ischæmia is accompanied by minimal paræsthesiæ.

Lewis, Pickering, and Rothschild showed that when the distal cuff alone is released, the whole limb remains ischæmic, and no paræsthesiæ are felt. It is thus the return of the circulation, and not the release of the pressure as such, which causes the paræsthesiæ. Again, it is possible to show that it is the duration of ischæmia, and not the duration of compression which determines the intensity of the paræsthesiæ.

The upper of two adjacent cuffs is inflated on the arm; ten minutes later the adjacent lower cuff is inflated and the upper cuff deflated. This release of the upper cuff is followed by restoration of the circulation only to a small proximal segment of the limb, with resulting mild paræsthesiæ in the hand. Five minutes later, when these have ceased, the lower cuff is released. The paræsthesiæ which follow are marked, and correspond in severity with those which normally follow fifteen minutes' ischæmia. It is the ischæmia in the distal part of the limb, of fifteen minutes' duration, which determines the severity of the paræsthesiæ, although the distal cuff has been compressing the limb for only five minutes.

It is important that the pressure in the cuff should be above systolic pressure; increasing it by increments of 25, 50, or 100 mm. Hg above systolic pressure does not alter the character or duration of the paræsthesiæ. In experiments with a clamp, in which the circulation is arrested in 12 cm. segments of limb, leaving the rest of the limb with a normal circulation, as in Experiment 11, pressures as low as 70 mm. Hg are adequate for the production of paræsthesiæ. But the maintenance of pressures below systolic level in a single cuff soon leads to great congestion of the veins and tissues distally, and the sensations resulting from this tend to make observations on true post-ischæmic paræsthesiæ difficult. However, paræsthesiæ of short duration do result from the release of a single cuff inflated to a pressure of 70 mm. Hg.

Post-ischæmic paræsthesiæ may be modified by altering the temperature of the limb. Placing the limb in a water-bath at 10° C. 5 minutes before applying the cuff causes a marked diminution in the tingling paræsthesia, and accentuates pricking. Unless otherwise stated, the experiments described in this study have been carried out at room temperature, at which the results obtained show little variation.

The Differentiation of Post-ischæmic Paræsthesiæ

We have already described the four types of paræsthesiæ which together make up the complicated sensations felt after release of the circulation to a limb. In differentiating them, we are concerned chiefly with the distinction between tingling and pricking, because they are most easily and frequently confused, and because they usually occur together. Thermal paræsthesiæ and pseudo-cramp are more distinct sensations, and consequently more readily recognized.

Thermal paræsthesiæ occur immediately after release, and end before other sensations are felt. In clinical cases in which temperature sense is lost in a limb, all forms of post-ischæmic paræsthesiæ may be induced in that limb except thermal paræsthesiæ (see Cases 4, 6, 7, and 8).

The sensation of *pseudo-cramp* also has a distinctive character. This paræsthesia commonly

occurs when other sensations are at their height; it is of some importance, therefore, to know that it may be felt by itself.

Experiment 3. (W.R.M.).—With a cuff applied to the arm as in Experiment 1, the circulation was arrested for ten minutes and released for thirty seconds; this cycle was repeated several times. After the fifth or sixth short period of release, the post-ischæmic paræsthesiæ differed from those after the first. Pseudo-cramp became the most prominent sensation; it began spontaneously about seventy seconds after release, lasted about a minute, and was then followed by very slight tingling and later by pricking. When the pseudo-cramp was present alone, tingling could be induced by touching the ventral surfaces of the fingers or hand, but if no such stimuli were applied the only sensation was a marked feeling of tension in the fingers, hand, and wrist.

By a suitable arrangement the radial nerve alone may be compressed in the arm. Release of the pressure on this nerve often results in a sensation of pseudo-cramp alone without the other forms of paræsthesiæ.

Experiment 4. (P.W.N.).—The forearm was rested on a padded table at shoulder height. A strap 5·5 cm. wide was placed over the arm 5 cm. above the lateral epicondyle, and the ends weighted with a 5-kg. weight. After twenty-five minutes there was hypo-æsthesia in the skin of the distribution of the superficial radial nerve, and weakness of the extensors of the thumb. The pressure was released after thirty minutes. Seventy seconds later pseudo-cramp was felt in the radial side of the wrist; it spread up over the back of the forearm, and when at its height, ten seconds later, was accompanied by involuntary contraction of the extensors of the wrist and thumb. The feeling of tension lasted a minute in all; no other paræsthesia occurred spontaneously, but tingling could be induced by touching the skin in the area supplied by the radial nerve.

Again, as Bazett and McGlone (1931) have pointed out, pseudo-cramp becomes the most prominent of the paræsthesiæ felt after an adequate period of ischæmia in a limb which has been immersed in water at 45° C. Other forms of paræsthesiæ are not correspondingly increased.

These experiments confirm that pseudo-cramp is a distinct form of post-ischæmic paræsthesia. It is to be noted that in Cases 8 and 9, referred to later, all paræsthesiæ except pseudo-cramp are felt in the limb in which position sense is absent.

The differentiation of *tingling and pricking* remains to be considered. It has already been stated that post-ischæmic sensations vary in different individuals. One form of variation is seen after minimal periods of circulatory arrest (five or ten minutes). In such experiments, some subjects feel only pricking, while others feel only tingling; a few feel both sensations.*

In subject W.R.T., for example, eight minutes was the minimum period of arrest necessary to produce any post-ischæmic paræsthesiæ, with the cuff applied above the elbow. Arrest lasting from eight to fifteen minutes resulted in pricking alone. After occlusions lasting over fifteen minutes, tingling was added to pricking though pricking outlasted it by several minutes. Twenty-five minutes' arrest was necessary to produce pseudo-cramp as well. In subject J.C., on the other hand, tingling was the most easily produced sensation. Arrest lasting from eight to ten minutes resulted in tingling alone. Fifteen minutes produced tingling and pricking, and still longer occlusions were necessary to produce pseudo-cramp as well.

The effects of repeated periods of occlusions have been referred to. They illustrate further differences between the tingling and pricking components of post-ischæmic paræsthesiæ.

After the fifth or sixth release in Experiment 3, tingling assumed a latent form; at first it was produced to an intense degree by touching the fingers or hand, but it did not appear spontaneously until a few minutes after release, and then only to a very slight degree. In this experiment, there was, in fact, a period when intense tingling was the only paræsthesia which could be induced; its vibrating character was easily noted, and no element of pain or pricking was observed. Transient pricking followed tingling.

A further distinction between tingling and pricking may be drawn from the different ways in which they are modified by altering the temperature of the limb. Pricking is considerably increased, and may be felt by itself if the limb is cooled throughout an experiment; there is also a tendency, though not so marked, for tingling to be increased when the limb is warmed. These effects are well seen after periods of ischæmia too short to produce pseudo-cramp.

They can be observed in all subjects; two examples are given, one in a subject in whom tingling normally outlasts pricking, and the other in a subject in whom pricking is usually the more prolonged paræsthesia.

Experiment 5. (P.W.N.).—Cuffs were applied to both forearms just below the elbows. The left forearm was immersed in a water-bath maintained at 40° C.,

* The problem of identifying the sensation which a subject feels has been given much attention. Paræsthesiæ are subjective. In the last instance, therefore, there is no way of proving what it is a particular subject feels. However, in the great majority of over thirty subjects examined by us it has been possible to identify with reasonable certainty the type of post-ischæmic paræsthesia being felt. The peripheral distribution of the sensation, its time of onset, the kind of procedure being employed to induce it, and the effect of stimuli on it, have all been of value in confirming the type of sensation suggested by the subject's own description of it.

and the right in a water-bath at 15° C. throughout the experiment. Both cuffs were inflated five minutes after immersion, and released after twenty minutes' ischæmia. Post-ischæmic paræsthesiæ were felt as follows :

Left arm (warm)	*Right arm (cold)*
Tingling began 55 secs. after release and lasted 185 secs.	Tingling began 85 secs. after release and lasted 65 secs.
Pricking began 85 secs. after release and lasted 55 secs.	Pricking began 90 secs. after release and lasted 240 secs.

Pricking, therefore was present alone in the cooled right hand for 3 minutes, while tingling outlasted pricking in the warmed left hand.

Further, in this subject (P.W.N.), ischæmia of only seven minutes' duration at 10° C. produced pricking but no tingling, whereas similar occlusions at room temperature invariably gave tingling alone.

Experiment 6. (W.R.M.).—The conditions of the experiment were as in Experiment 5. Post-ischæmic paræsthesiæ resulted as follows :

Left arm (warm)	*Right arm (cold)*
Tingling began 70 secs. after release and lasted 280 secs.	Tingling began 80 secs. after release and lasted 220 secs.
Pricking began 40 secs. after release and lasted 110 secs.	Pricking began 65 secs. after release and lasted 540 secs.

Here again, pricking outlasted tingling in the cooled right hand, while tingling was more prolonged in the left. In this subject, short periods of ischæmia at room temperature invariably gave pricking alone, whereas short periods of ischæmia at 40° C. give tingling alone.

The results of Experiments 5 and 6 are illustrated diagrammatically in Fig. 3.

One may conclude from these experiments that, although tingling and pricking usually occur together, they are two distinct forms of post-ischæmic paræsthesiæ.

The Site of Origin of the Paræsthesiæ

In discussing the origin of the nerve impulses felt as post-ischæmic paræsthesiæ, the sensory pathway may be divided into three parts : the end-organs, the nerves distal to the cuff, and the nerves directly beneath the cuff. The part each plays in the production of paræsthesiæ is demonstrated by means of experiments now to be described.

There is ample evidence to show that sensory end-organs are not essential for the production of post-ischæmic paræsthesiæ. In the first place, paræsthesiæ may be induced in a subject with an amputation provided there is no damage or degeneration of the nerve trunks at the level of the cuff ; the paræsthesiæ are felt in the phantom hand or foot, and have their usual characteristics.*

Case 1.—Pte. F., a sniper, was wounded in the left forearm in July, 1944, and had an amputation through the lower forearm three weeks later. He was examined in March, 1947. A cuff was placed above the left elbow, 38 cm. above the stump, and inflated for twenty-five minutes. After this was released he felt tingling and pricking starting in the fingers and back of the phantom hand, and later a feeling as though the wrist was being forced into flexion. Tingling lasted six minutes, pricking about four minutes, and the feeling of flexion just over three minutes. After release of a similar length (38 cm. measured from the finger-tips) of the right arm, paræsthesiæ of the same type, but of slightly longer duration, were felt.

* The common practice of dividing large nerve trunks as high as possible and crushing them during amputations makes it difficult to judge the level at which functioning nerve fibres end. It is certain that this level is often several inches above the stump, and it is therefore not surprising that paræsthesiæ frequently cannot be induced in such cases by compression with a cuff. The fact that they can be induced in some cases, however, is all that is relevant to the present argument.

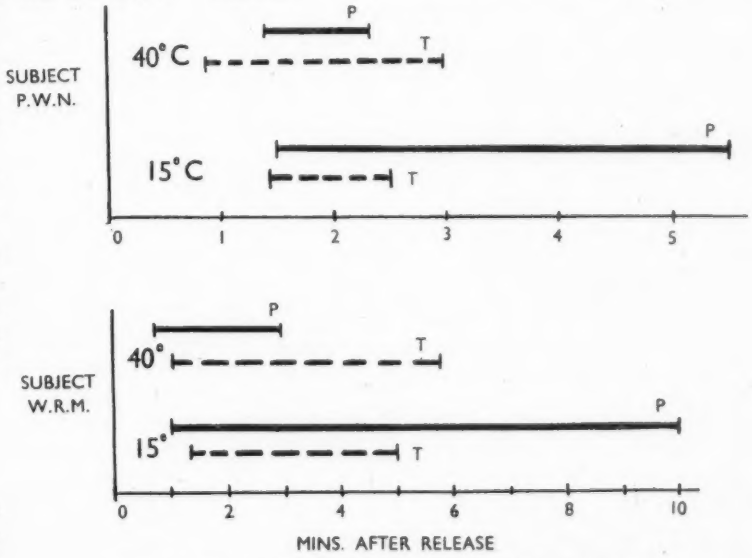


FIG. 3.—Diagram illustrating the effect of temperature on the duration of tingling (T) and pricking (P) in two subjects. (Cuffs below the elbows ; twenty minutes' ischæmia).

Paræsthesiæ may also be induced in the anæsthetic area in subjects with a complete peripheral nerve lesion provided the occluding cuff is placed above the lesion.

Case 2.—A patient had a complete lesion of his left median nerve just proximal to the wrist. At operation the injured segment of the nerve was resected and the ends re-sutured. At the time of the experiment, four weeks later, there was no sign of recovery ; Tinel's sign was negative. Cuffs were placed above the elbows and inflated for fifteen minutes. After release, paræsthesiæ were felt concurrently in both hands ; no difference was detected by the subject between the paræsthesiæ in the median and those in the ulnar areas of the affected hand.

In this case, the median sensory end-organs had no functional connexion with the central nervous system. Comparable results have been obtained in two other patients with complete ulnar nerve lesions at the wrist. These findings have been supported by inducing post-ischæmic paræsthesiæ when the nerves from the areas in which the paræsthesiæ are felt have been completely blocked by local anæsthetic distal to the occluding cuff. The following experiment illustrates this.

Experiment 7. (P.W.N.).—Procaine hydrochloride was injected into the median and ulnar nerves just above the wrist, producing a complete median and ulnar block. A cuff was then placed above the elbow and inflated for thirty minutes. After release, all three paræsthesiæ (tingling, pricking, and pseudo-cramp) were felt in the hand, thumb, and fingers, although these areas remained anæsthetic throughout the experiment and for some hours afterwards.

The following experiment excludes the cutaneous end-organs from taking part in the changes which result from release of the circulation, and demonstrates again that paræsthesiæ may occur without the participation of these end-organs.

Experiment 8.—One hand was immersed for a few seconds in a solution of 8 per cent. celloidin in equal parts of ether and alcohol. On withdrawal, the hand and fingers were coated with a thin transparent layer of celloidin which slowly contracted as it dried, so that after about fifteen minutes the fingers and much of the palm and dorsum of the hand developed an intense pallor resulting from ischæmia of the skin and subjacent tissues. Both hands were immersed in a water-bath at about 30° C. to equalize their temperatures, and cuffs were then inflated above both elbows. After twenty minutes the cuffs were released. The circulation was rapidly restored to the whole of the control limb, but in the hand coated with celloidin the fingers and most of the hand remained completely blanched and showed no sign of a return of circulation. In spite of this gross difference, paræsthesiæ of simultaneous onset and of equal intensity and duration were felt in the two hands.

The experiments just described (Cases 1 and 2, and Experiments 7 and 8) demonstrate clearly that the three forms of paræsthesiæ may all be induced without difficulty under conditions in which sensory end-organs can play no part. In these experiments the impulses felt as paræsthesiæ must, therefore, have arisen in the nerves. It does not necessarily follow that the end-organs contribute nothing to the sensations resulting from recovery of the circulation to the whole limb. The results of Experiment 8 do suggest that their contribution, if anything, is a small one ; there is no detectable difference between the paræsthesiæ resulting from release of the upper limb when the hand is included, and when it is not. More direct evidence on this point is provided by a further experiment with celloidin, in which the cutaneous end-organs of the hand are rendered ischæmic without involving significant stretches of nerves at the same time. Under these conditions, it may be shown that recovery of the skin from prolonged ischæmia does not produce paræsthesiæ.

Experiment 9.—The hand and fingers were coated with celloidin as described in Experiment 8. After the ischæmia produced by this method had continued for forty minutes the celloidin was rapidly removed by immersing the hand in a vessel of solvent ; within twenty seconds normal colour returned to the fingers and hand, but this recovery from ischæmia did not result in the appearance of paræsthesiæ.

In another experiment the celloidin coat was quickly dissolved from the tip of one of the constricted fingers ; a prompt return of the circulation to the finger-tip showed that the main digital arteries were not occluded by the pressure of the celloidin. It was probable, therefore, that only the most superficial of the sensory structures in the finger, that is, the cutaneous end-organs, were involved in this marked visible ischæmia.

Paræsthesiæ may also be felt after release of a cuff placed on the proximal part of a limb, even though the circulation remains arrested to the distal areas in which the paræsthesiæ are felt. Under these conditions the relevant sensory end-organs can play no part in producing sensations due to the returning circulation.

Experiment 10. (W.R.M.).—Cuff A was placed with its lower edge 5 cm. above the wrist, cuff B was placed as high as possible on the same arm, and both were inflated. After thirty minutes cuff B was released. Tingling, pricking, and pseudo-cramp were felt in the fingers, hand, and wrist, although these parts remained ischæmic for as long as cuff A was allowed to remain inflated.

It may be concluded that in this experiment tingling and pricking were not caused by events

taking place in the hand or fingers. The case of pseudo-cramp, however, demands special consideration, for it might be argued that this sensation, although referred distally, could arise in the deep structures of the forearm, for example in muscles which normally produce movements of the fingers and wrist. The following experiment shows that muscle afferent end-organs do not play an essential part in the production of the feeling of tension.

Experiment 11. (W.R.M.).—Cuff A was placed on the elbow and cuff B as high as possible on the same arm. Both cuffs were inflated. When cuff B was released after thirty minutes' ischæmia, the first and most severe paræsthesia was pseudo-cramp in the wrist and hand; other paræsthesiæ were also felt. The limb remained ischæmic distal to the elbow.

In this experiment it is assumed that between the two cuffs there were no muscle afferent end-organs capable of causing sensations felt in the wrist or hand.

It may be concluded from these experiments that sensory end-organs are not the site of origin of impulses felt as post-ischæmic paræsthesiæ.

Experiments may also be devised which show that the nerves distal to the occluding cuff are not essential for the production of post-ischæmic paræsthesiæ. Some of these experiments were described by Lewis, Pickering, and Rothschild; the conclusions these authors drew from their results will be discussed later. Experiment 11 may be modified so that the two cuffs are adjacent. Release of the upper cuff now restores the circulation only to segments of the nerves directly beneath it, the nerves distal to it remaining ischæmic. Paræsthesiæ, nevertheless, do result, although they are less severe and of shorter duration than those resulting from the return of the circulation to the whole limb. As usual, they are felt in the hand and fingers. The following is an example of such an experiment.

Experiment 12. (M.S.).—Two cuffs were inflated adjacent to each other, above the left elbow. After twenty minutes the upper cuff alone was released, thereby restoring the circulation to a segment of arm 12 cm. long. Paræsthesiæ of the following duration were felt in the hand:

Tingling:	Onset 130 secs. after release; Duration 6 mins.
Pricking:	Onset 90 secs. after release; Duration 3 mins.
Pseudo-cramp:	Onset 150 secs. after release; Duration about 5 secs.

A control experiment, performed by releasing the circulation to the whole of the right arm, resulted in paræsthesiæ of slightly more rapid onset, of much greater intensity, and of longer duration:

Tingling:	Onset 80 secs. after release; Duration over 8 mins.
Pricking:	Onset 50 secs. after release; Duration 6 mins.
Pseudo-cramp:	Onset 70 secs. after release; Duration 2 mins.

That post-ischæmic paræsthesiæ may be induced by local compression and release of short segments of limb was also shown by Lewis, Pickering, and Rothschild, by means of a special clamp. Briefly, the clamp is an apparatus with which short lengths of some of the main nerves in the arm can be compressed without stopping the circulation to the distal part of the limb. These authors showed that paræsthesiæ, felt in the hand, followed the release of pressure with this clamp. The following experiment compares the duration of paræsthesiæ induced by cuff and by clamp.

Experiment 13. (P.W.N.).—A clamp 12 cm. wide was applied to one arm above the elbow, and a cuff was placed on the other arm at the same level. Both were inflated for twenty-five minutes and then released simultaneously. Paræsthesiæ of the following duration were felt:

	Clamp	*Cuff*
Pseudo-cramp:	30 secs.	80 secs.
Pricking:	115 secs.	270 secs.
Tingling:	190 secs.	over 720 secs.

The sensations were much less severe on the side of the clamp.

As a rule, both the median and ulnar nerves are compressed when the clamp is applied above the elbow; after release, paræsthesiæ are felt in the corresponding areas of the hand. If, in a particular subject or experiment, only the median nerve is compressed, as judged by the distribution of the resulting anæsthesia, then the post-ischæmic paræsthesiæ are confined to the median area of the hand.

It can be shown in the following manner that only those parts directly compressed by the clamp are rendered ischæmic by it, and that the nerves distal to it are unaffected.

Experiment 14. (W.R.T.).—The clamp was applied to the arm and inflated to 70 mm. Hg. for twenty minutes, by which time there was marked hypoæsthesia in the finger-tips. A cuff placed immediately distal to the clamp was then inflated, and a control cuff was simultaneously inflated in a similar position on the other arm. The clamp was released, leaving the cuffs inflated; the anæsthesia caused by the clamp quickly cleared up and there followed the usual paræsthesiæ resulting from its release. In the course of the ensuing twenty minutes, anæsthesia due to the

cuffs developed in both hands at exactly the same rate. Moreover, after their release at the end of this time, paræsthesiæ of the same intensity, type, and duration were then felt in the two hands.

We have here a clear indication that the nerves distal to the clamp had been unaffected by its application over a period of twenty minutes, and that they afterwards reacted in exactly the same way as those in the control limb.

By blocking the main nerves at the wrist, it can also be shown that the sensory end-organs in the hand play no part in the production of post-ischæmic paræsthesiæ resulting from release of the clamp.

Experiment 15. (P.W.N.).—The left median and ulnar nerves were injected with procaine and adrenaline 2 cm. above the wrist. Complete median and ulnar paralysis and anæsthesia followed. The clamp was applied to the arm and inflated to 70 mm. Hg. for twenty minutes, during which time the circulation in the hand remained apparently normal. After release of the clamp, paræsthesiæ of the following duration were felt in the anæsthetic hand and fingers.

Tingling : Onset 65 secs. after release ; Duration 145 secs.

Pricking : Onset 105 secs. after release ; Duration 125 secs.
No pseudo-cramp was felt.

In experiments with the clamp, then, neither the sensory end-organs nor the nerves distal to the segment compressed contribute to the production of paræsthesiæ. Impulses felt as paræsthesiæ must, therefore, arise in the larger nerves directly beneath the clamp, when the circulation is restored to them.

By blocking the main nerves with local anæsthetic just distal to a cuff, all sensory effects resulting from return of the circulation to the distal parts of the limb can be excluded. Under such conditions, post-ischæmic paræsthesiæ are still felt ; it follows, therefore, that the impulses responsible for these sensations originate in the nerves directly underneath the cuff. In carrying out such an experiment, the cuff must be placed a sufficient distance above the point of injection to allow for the spread of local anæsthetic along the nerves. In early experiments, the median and ulnar nerves were blocked at the elbow and the cuff applied immediately above the points of injection ; release of the cuff was not followed by paræsthesiæ. Simple tests with an electrode suggested that there was an extensive spread of local anæsthetic up the nerve trunks, so that the cuff, applied about twenty minutes later, was in fact compressing anæsthetized nerve. For example, when 2 c.cm. of 2 per cent. procaine with adrenaline was injected into the ulnar nerve at the wrist, this nerve was soon found to have become anæsthetic to strong faradic stimulation for at least 8 cm. above the point of injection.

From the experiments described it would at first seem reasonable to conclude that impulses responsible for post-ischæmic paræsthesiæ arise in those parts of the nerves actually compressed by the cuff. There is adequate proof that they can be produced without sensory end-organs and without functioning nerve trunks distal to the compressed segment. But it is important to remember that in all these experiments the longer the length of nervous tissue recovering from ischæmia the more marked and more prolonged are the paræsthesiæ. These facts are shown diagrammatically in Fig. 4. It seems unlikely, therefore, that these impulses arise solely from beneath the cuff in experiments in which the circulation is restored to the whole limb.

In order to investigate this point, many experiments have been conducted comparing the duration of post-ischæmic paræsthesiæ resulting from the release of different lengths of nerve. Two methods have been employed. In the first, a single cuff was released at different levels in the arm and forearm, the length of nerve involved being estimated by measuring the distance from the upper edge of the cuff to the middle finger-tip. In the second, two cuffs were used, one placed high on the arm and the other at different distances below it ; release of the upper cuff thereby restored the circulation to different lengths of nerve. When the cuffs were adjacent, only 12 cm. (the width of a cuff) of nerve was released ; if the cuffs were separated, longer lengths of nerve had their circulation restored. Tables I and II give the results obtained by the two methods.

The effect of releasing less than 12 cm. of nerve can be studied by overlapping the cuffs or by the use of weighted bands or other hard objects which can be made to press on a single nerve. It has been found that when less than 2 cm. of a nerve is compressed, even for periods long enough to cause anæsthesia, release is never followed by paræsthesiæ.

It is seen that after a constant period of ischæmia release of the circulation results in paræsthesiæ which are more severe when a greater length of nerve is involved. Two explanations of this fact may be considered. First, all parts of the nervous pathway concerned may be capable of contributing more or less equally to the paræsthesiæ ; each part of the affected nerve would add its increment to the resulting sensations, so that a greater length of released nerve would produce a more marked result. Alternatively, the more proximal parts of the nerves might be more sensitive to return of the circulation ; the longer lengths of nerve necessarily include the more proximal parts and would therefore produce

Release of single cuff above elbow restores circulation to whole limb and is followed by marked paræsthesiæ felt in the hand (Expt. 1).

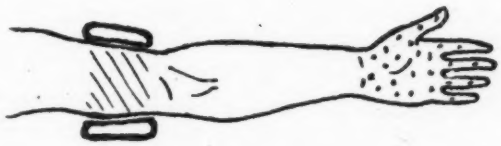
Amputation at wrist. Release of cuff is followed by paræsthesiæ in phantom hand (Case 1),

Complete nerve-block or nerve lesion at wrist. Release of single cuff is followed by paræsthesiæ felt in the hand (Case 2, Expt. 7).

Lower cuff at wrist remains inflated. Release of upper cuff is followed by paræsthesiæ felt in the hand (Expt. 10).

Lower cuff above elbow remains inflated. Release of upper cuff is followed by slight paræsthesiæ felt in the hand (Expt. 11).

Complete nerve block at elbow. Release of cuff is followed by slight paræsthesiæ felt in the hand (page 10).



Clamp applied above elbow. Release is followed by slight paræsthesiæ felt in the hand (Expt. 13).

Areas to which the circulation is restored.

Areas in which the paræsthesiæ are felt.

FIG. 4.—Diagram summarizing the results of experiments relating to the site of origin of impulses felt as paræsthesiæ.

more marked paræsthesiæ. The second hypothesis was that favoured by Lewis, Pickering, and Rothschild, but it is one which we are unable to confirm. In the first place, Table II shows results which clearly indicate that the inclusion of distal parts of the nerve adds considerably to the duration (and severity) of the paræsthesiæ. Again, the sensitivity of the nerves at different levels in the limb can be tested by further experiment.

TABLE I

DURATION OF PARÆSTHESIÆ FOLLOWING 40 MINUTES' ISCHÆMIA PRODUCED BY A SINGLE CUFF AT DIFFERENT LEVELS IN UPPER LIMB (P.W.N.).

Position of cuff, (cm., from middle finger-tip)	Average Duration of paræsthesiæ (secs.)		
	Tingling	Pricking	Pseudo-cramp
Upper arm (68 cm.)	930	510	120
Lower arm (63 cm.)	730	170	100
Upper forearm (49)	640	130	50
Lower forearm (33)	200	120	20

TABLE II

DURATION OF PARÆSTHESIÆ FOLLOWING RELEASE OF UPPER CUFF, WITH LOWER CUFF AT DIFFERENT DISTANCES BELOW IT (UPPER LIMB, 20 MINUTES' ISCHÆMIA) (W.R.M.).

Length of limb released (distance between upper edges of cuffs)	Average duration of paræsthesiæ (secs.)		
	Tingling	Pricking	Pseudo-cramp
63 cm. (whole limb) . .	690	480	80
29 cm. (hand excluded)	570	480	60
19 cm.	370	180	Nil
12 cm. (width of a cuff)	320	120	Nil

Experiment 16. (Consisting of several similar experiments).—Two cuffs were applied, adjacent to each other. In the different experiments the position of these two adjacent cuffs was varied, so that different parts of the limb were compressed. By releasing only the proximal cuff, the circulation was restored to stretches of nerve 12 cm. long at different levels. It was found that the release of such segments produced paræsthesiæ of fairly constant duration and severity, wherever the cuffs had been placed. Although the duration of paræsthesiæ in these experiments was not always the same, there was no constant tendency for the paræsthesiæ to last longer after releasing more proximal segments.

It may be concluded, then, that post-ischæmic paræsthesiæ result from recovery in all parts of a nerve, and that when the whole limb is recovering from ischæmia all parts of the nerve contribute to the resulting sensations. It must be admitted that these facts do not appear to apply to all the nerves in a limb. In experiments of moderate duration performed on the arm, tingling and pricking are invariably felt only in the palm of the hand and fingers, indicating that the median and ulnar nerves are chiefly involved. The recovery of considerable lengths of other sensory nerves (the cutaneous nerves of the forearm, for example) is not associated with paræsthesiæ felt in their areas of distribution. Yet, as we have seen, the recovery of quite short lengths of median and ulnar nerves at any level in the arm results in paræsthesiæ felt in the palm and fingers. Problems arising from these conflicting observations will be referred to again.

The Nerve Fibres Conducting the Paræsthesiæ

The results of experiments on different subjects have led us to believe that the impulses interpreted as the three paræsthesiæ, tingling, pricking, and pseudo-cramp, arise and are conducted in the nerve fibres normally concerned with the senses of touch, pressure, movement, and position. They are not conducted in sympathetic fibres, or in those concerned with the senses of pain, warmth, or cold. The evidence for these views follows.

With the special clamp already referred to, a progressive anæsthesia can be produced in the hand, resulting from local changes in the compressed nerve trunks ; the circulation to the arm and hand meanwhile remains undisturbed. Following the application of the clamp, different forms of sensation are lost in the fingers and hand at different rates, cold and pain being the last to go.* In a partial nerve block of this type, inflation and release of a cuff placed distal to the clamp will only cause paræsthesiæ if the nerve fibres conducting them remain unblocked. If the clamp has been in position too long, there will be complete loss of all forms of sensation in the hand at the time the cuff is released, and no paræsthesiæ will be felt. Similarly, by releasing the cuff when only pain and cold senses still remain in the hand, it can again be shown that no paræsthesiæ are felt. The following experiment is given in illustration.

Experiment 17. (W.R.T.).—A clamp was applied to the left arm. A cuff was applied just distal to it, and a control cuff placed on the right arm at the same level.

* For detailed accounts of this progressive centripetal anæsthesia, the articles by Lewis, Pickering, and Rothschild (1931), and by Lewis and Pochin (1938) may be consulted.

0 *minutes.* Clamp inflated to 70 mm. Hg. Circulation at the wrist remained normal.

6 *minutes.* Both cuffs inflated to 200 mm. Hg.

26 *minutes.* Sensation tested in the left hand. From the wrist downwards there was complete loss of touch, pressure, and warmth senses; position sense in the little finger was absent. There was no loss to pain sense as tested by pinprick, but this stimulus, when applied to the fingers, caused a delayed and unusually painful sensation which could not be localized. Cold sense was present in the palm but not in the fingers.

28 *minutes.* Both cuffs were released; the clamp remained inflated. Reactive hyperæmia developed equally in both hands. Paræsthesiæ, lasting seven minutes in all, were felt in the right (control) hand. No paræsthesiæ were felt in the left hand.

35 *minutes.* Sensation again tested in the left hand. The only significant change from the previous test was that the area of modified pain sense had extended to the palm.

Fig. 5 illustrates this experiment, which shows that the paræsthesiæ did not arise or travel in the nerve fibres subserving the senses which remained in the left hand, that is, in cold or pain fibres.

By inflating the clamp and cuff together in this experiment, a nerve block results which is less complete by the time the cuff is released. Provided some tactile sense then remains in the hand, paræsthesiæ will be felt. These results have been confirmed on many occasions, but, using this method of producing a partial nerve block, we have not been able to establish a clearer relationship between the type of sensory loss and the form of paræsthesia which is blocked. For it has been our experience that the various forms of sensation (except for pain and cold) are lost so nearly simultaneously that prolonged observation at a chosen level of anæsthesia is difficult.

When a local anæsthetic is injected near a nerve trunk, there follows a partial nerve block which differs in certain important respects from that caused by the pressure of the clamp. Sympathetic and pain-conducting fibres are paralysed first, fibres subserving temperature senses next, and only later are those subserving touch affected. With care it is possible to induce partial anæsthesia which remains in the same state for several hours. Here again, compression and release of a cuff placed distal to such a nerve block will produce post-ischæmic paræsthesiæ in the area supplied by the nerve, only if those fibres conducting the paræsthesiæ are still functioning. The results of several experiments have shown that tingling, pricking, and pseudo-cramp may still be felt when sympathetic fibres are paralysed, and when pain, warmth, and cold senses are completely blocked.

Experiment 18. (W.R.M.).—Two per cent. procaine with adrenaline was injected near the median nerve just above the right elbow. A partial nerve block developed so that half an hour later the skin was hot and dry in the median area, and there was complete loss of pain (pinprick), warmth and cold, and light touch (cotton wool); heavier touches were felt. A cuff was inflated on the forearm just distal to the point of injection, and was released after fifteen minutes. The initial temperature paræsthesiæ were not felt in the median area, but subsequently tingling and pricking were both felt over the whole hand and lasted for five minutes. The only detectable difference between these paræsthesiæ in the median and ulnar areas was that the onset of pricking was slightly delayed in the median area. After the paræsthesiæ had subsided, sensation in the hand was again tested and found to be unchanged, apart from slight recovery of light tactile sense; there was still a total pain, temperature, and sympathetic block in the median area. In this experiment, the period of circulatory arrest employed (fifteen minutes) was insufficient to induce pseudo-cramp. (This form of paræsthesia has been felt after longer periods of arrest distal to a similar nerve block.)

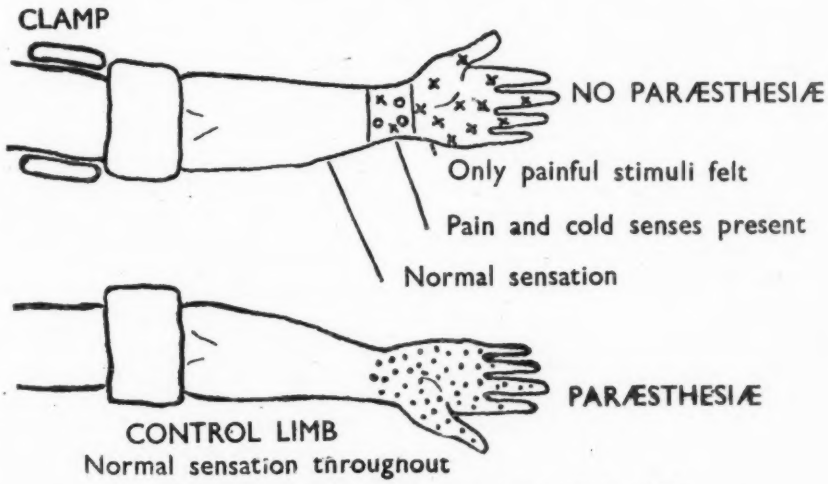


FIG. 5.—Diagram illustrating Experiment 17, in which a clamp maintains a partial nerve block and also stops the conduction of paræsthesiæ.

From the results obtained with these two methods of partial nerve block, certain types of nerve fibre can be excluded as possible pathways in which the paræsthesiæ are conducted. Clamp experiments show that post-ischæmic paræsthesiæ (except thermal paræsthesiæ) do not run in fibres subserving cold or pain; chemical block experiments show that these paræsthesiæ are not conducted in the fibres subserving pain, warmth, or cold, or in the sympathetic fibres.*

Lewis, Pickering, and Rothschild observed that when post-ischæmic paræsthesiæ were at their height, tactile stimuli applied to the affected areas increased the sensations, whereas other stimuli (temperature and pinprick) had no effect on them. They suggested, therefore, that the fibres subserving the sense of touch were also concerned in the production of the paræsthesiæ. We were able to confirm and extend their observations by studying the effect of stimuli on the various individual forms of paræsthesiæ.

The following methods of applying stimuli were employed.

Warmth was applied by radiant heat, using a modification of the instrument described by Stone and Dallenbach (1934). Cold stimuli were provided by the use of an ethyl chloride spray. Touch was applied with von Frey's hairs or with a wisp of cotton wool. Pressure was applied with a pencil, a pin's head, or observer's fingers. Painful stimuli were produced by pinprick. The initial effects of contact of the pin with skin were ignored, as pain was then complicated by stimulation of the tactile sense; further pressure with the pin gave a purer painful stimulus.

These stimuli were applied to the areas in which isolated forms of paræsthesiæ were being felt. Touch or movement sufficient to deform the skin increases the intensity of tingling. Considerable pressure which meets with firm resistance from the bones of the hand or fingers increases pricking. Active or passive movements of the fingers or wrist increase the feeling of tension. These stimuli also induce the corresponding paræsthesiæ under conditions already described in which the sensations are " latent " (see Experiment 3). Painful stimuli, warmth, cold, and very light tactile stimuli are all without effect on the paræsthesiæ.

The effects of certain stimuli on the areas on which paræsthesiæ are being felt may be tested in another manner. When a cuff applied to the arm arrests the circulation for about an hour, there is loss of all forms of sensation distally except that of pain. At this stage, a second cuff is applied just distal to the first, and the first cuff is released. A partial recovery of some forms of sensation occurs, and at the same time marked paræsthesiæ are felt in the hand. In effect, there is a partial nerve block distal to a stretch of nerve recovering from ischæmia. Areas can thus be prepared in which post-ischæmic paræsthesiæ are felt, but which are sensitive only to warmth, cold, or painful stimuli. These stimuli can be applied uncomplicated by any tactile or pressure stimulus; they are without effect on the paræsthesiæ, as the following experiment shows.

Experiment 19. (P.W.N.)—A cuff was applied above the elbow and inflated to 200 mm. Hg. An hour later the entire limb distal to the cuff was insensitive to all forms of stimuli except painful ones. A second cuff was inflated immediately below the first, which was then released. This produced the usual paræsthesiæ in the hand and wrist. While they were being felt, various stimuli were applied to the hand, but none had any effect on the paræsthesiæ; painful stimuli were the only ones to be felt. Ten minutes later the procedure was repeated; a third cuff was inflated just below the second, and the second cuff was released. Again the usual paræsthesiæ followed, and again the effect of stimuli on them was tested. In the lower forearm and wrist, skin-deforming touch, pressure, and movement increased the paræsthesiæ; stimulation everywhere distal to the wrist had no effect. In the forearm and wrist all forms of sensation had recovered, but distal to this, only pain, warmth, and cold were felt.

The interpretation of these results rests, of course, on the assumption that a paræsthesia which is increased by stimulation of a certain sense, is conducted in the nerve fibres normally concerned with that sense.

Evidence so far presented suggests, then, that the tingling element of post-ischæmic paræsthesiæ arises and is conducted in those fibres subserving touch (but not the lightest touch sensation induced by stroking with a hair), that pricking is conducted in those fibres subserving a sense of firm pressure, and that pseudo-cramp is conducted in those fibres subserving the sense of movement. By exclusion the evidence clearly shows that these three paræsthesiæ are not conducted in sympathetic fibres, or in those subserving the sensations of warmth, cold, and pain.

Additional proof that sympathetic fibres are not concerned can be provided in experiments on patients with sympathectomized limbs. In such patients, the usual post-ischæmic paræsthesiæ appear to be unaltered by interruption of the sympathetic pathways. The following case is an example.

Case 3.—A man aged 55 had suffered from symmetrical Raynaud's disease of his hands for six years. A right

* In experiments involving a partial block with the clamp, the appreciation of painful stimuli has been accepted as evidence that pain sense is present; no attempt has been made to distinguish between 'first pain' and 'delayed pain.' In the experiments with procaine block, pain sense as a whole is absent.

preganglionic cervical sympathectomy was performed. At the time of the experiment two weeks later there was complete sympathetic paralysis below the right elbow. Cuffs were applied to both arms and inflated for twenty minutes. Ischæmic paræsthesiæ, and, after release, post-ischæmic paræsthesiæ were felt in both hands; no difference was noted between the sensations on the two sides, except that the moment of maximum intensity on the right side occurred earlier than on the left. The duration of post-ischæmic paræsthesiæ was four minutes on both sides.

The Central Nervous Pathways Conducting the Paræsthesiæ

Evidence relating to the pathways concerned in the conduction of post-ischæmic paræsthesiæ has been sought from experiments on patients with lesions of the central nervous system. Several patients have been examined in whom there has been interruption of tracts subserving pain and temperature. The simple experiment of occluding the circulation first to a normal limb was performed on these patients so that they could learn to distinguish the three paræsthesiæ. The forms of paræsthesiæ felt in the limb from which some sensory pathways are blocked depend on which tracts remain normal. Thus if a lesion blocks a tract in which the paræsthesiæ are not conducted, normal paræsthesiæ will be felt; but if a lesion blocks a tract in which a paræsthesia is conducted, this paræsthesia will not be felt. The results conform with the findings already recorded, and show that post-ischæmic paræsthesiæ are not conducted in tracts subserving pain and temperature, but in those subserving touch and position senses. Evidence of a similar kind has been obtained suggesting that pseudo-cramp in particular is conducted in tracts concerned with the sensations of movement, position, and vibration.

Case 4.—A man, under the care of Sir Charles Symonds, had a thrombosis of the left posterior inferior cerebellar artery. At the time of the experiment, two months later, there was loss of appreciation of warmth, cold, and pain on the right limbs, and no sensory abnormality on the left limbs. Cuffs were placed above his elbows and inflated for thirty minutes. On release, the first sensation, one of heat, which was felt on the normal left hand, was not felt on the right; otherwise all paræsthesiæ (tingling, pricking, and pseudo-cramp) were felt equally on the two sides.

Case 5.—A man under the care of Dr. E. A. Carmichael had a thrombosis of the left posterior inferior cerebellar artery. Three months later the sense of pain, which was tested by pinprick or by squeezing the muscles, and the senses of warmth and cold were absent in the right limbs, although the senses of touch, position, movement, and vibration were all present; all forms of sensation were normal in the left limbs. Cuffs were placed above the knees and inflated for thirteen minutes. On release, tingling and pricking were felt in both feet, although they lasted longer in the left. Again, cuffs were placed above the elbows and inflated for thirty minutes; after release, tingling, pricking, and "gripping cramp" were felt in both hands, although for a short time they were more marked on the left.

Case 6.—A woman, under the care of Sir Charles Symonds, suffering from syringomyelia, had complete loss of pain and temperature sense over the right side of her face, right arm, and right trunk down to the level of the ninth dorsal segment; she had no other sensory loss. Cuffs were placed above the elbows and inflated for thirty minutes. After release she felt the initial thermal paræsthesiæ only on the left side; she felt all the other paræsthesiæ in both hands, and was unable to detect any difference between the sensations on the two sides.

Case 7.—A man had a bilateral upper dorsal cordotomy performed for painful tuberculous cystitis. Six weeks later, it was apparent that the interruption of the pain and thermal pathways was complete only on one side. In the left lower limb there was complete loss of pain, warmth, and cold sense; there was no loss of tactile, vibration, movement, or position senses; in the right lower limb there was slight loss of pain sense of uneven distribution, but thermal, tactile, movement, and position senses remained normal. Cuffs were applied above both knees and inflated for thirty minutes. After release, pricking and tingling were felt in both feet. There was an initial "hot feeling" on the right side, which was not noticed on the left. Pricking started and ended at the same time, and was of equal intensity on the two sides; tingling was of the same intensity, but lasted one minute longer on the right (eleven minutes).

In spite of complete interruption of the pain and thermal pathways on one side, all these four subjects felt the usual paræsthesiæ (tingling, pricking, and pseudo-cramp) in the affected limbs; it may be concluded, therefore, that the impulses giving rise to these sensations travel in the remaining intact sensory tracts, that is, in the posterior columns of the cord.

The following cases provide evidence relating to the conduction of the impulses felt as pseudo-cramp.

Case 8.—A man, under the care of Dr. E. A. Carmichael, had suffered an injury to his spinal cord at the level of the eleventh dorsal segment, which had caused a Brown-Séquard syndrome. Over the whole of his left lower limb he had complete loss of the sensations of pain and temperature; touches with cotton wool were not always appreciated, but the senses of position and movement were normal. In his right lower limb he had loss of the senses of position and movement in all toe and ankle joints, and over the entire limb there was loss of vibration sense; other senses were normal. Cuffs were placed on his thighs and inflated for thirty minutes.

After release, the following paræsthesiæ were felt :

Left	*Right*
(Pain and temperature absent)	(Position sense absent)
No thermal paræsthesiæ.	Feeling of heat.
Feeling of tension.	No feeling of tension.

Tingling and pricking were felt on both sides, but lasted slightly longer on the right.

It is to be noted that there was no feeling of tension on the side in which there was gross impairment of position, movement, and vibration senses, but that tingling and pricking were felt on both sides. Interruption of the pain and temperature pathways suppressed only the initial temperature paræsthesiæ.

Case 9.—A young doctor suffered from disseminated sclerosis. In both his upper limbs there was complete absence of vibration sense, and there was some loss of position sense in the fingers. Tactile sense was normal when tested with cotton wool, although very slight diminution could be demonstrated with von Frey's hairs. Pain and thermal senses were normal. Cuffs were applied above both elbows and inflated for thirty minutes. After release, tingling and pricking were felt to a marked degree in both hands. There was no feeling of tension on either side.

In this case, pseudo-cramp was the only paræsthesia which was not felt ; this was associated with a lesion blocking the pathway which normally conducts the sensation of vibration and the sense of position of the fingers.

Discussion

Experimental evidence has been presented which shows that the impulses felt as post-ischæmic tingling, pricking, and pseudo-cramp arise in the larger nerves of a limb. Reid (1931) and, more recently, Weddell and Sinclair (1947) concluded from their investigations that post-ischæmic pricking did not arise in the nerves but in certain peripheral nerve-endings. Such a deduction does not appear to be valid in the light of the experimental results obtained in patients with amputated limbs and with peripheral nerve lesions (Cases 1 and 2), for in such experiments peripheral nerve-endings were clearly incapable of contributing to any of the forms of paræsthesiæ.* Moreover, in the experiment with celloidin (Experiment 9), ischæmia of the fingers and hand which, it may be assumed, involved only the end-organs, was not followed by any form of paræsthesiæ.

It has been shown that post-ischæmic paræsthesiæ are more severe when longer lengths of limbs are released ; it is believed that this is because all parts of the larger nerves in a limb, except the nerve-endings, appear to be the site of origin of impulses felt as paræsthesiæ. In this respect, our findings have not confirmed the suggestions of Lewis, Pickering, and Rothschild, who stated that changes in the most proximal part of the nerves are largely responsible for the sensations. These authors considered that the sensations following release of the circulation showed certain resemblances to the centripetal anæsthesia which develops during ischæmia in a limb. For example, they found that the region of a nerve in which conduction is most depressed during ischæmia is the most proximal part (beneath the cuff). The state of this segment of nerve alone therefore determines the degree of anæsthesia observed ; lesser degrees of block present in more distal parts of the nerve are of no consequence. On the same basis, they believed that the most proximal part of the nerve is likewise the most sensitive to a return of the circulation, and is therefore the site of origin of the paræsthesiæ. It must be pointed out that, although the proximal segment of a nerve is one of the places where impulses arise spontaneously, this segment of nerve is still capable of conducting impulses felt as paræsthesiæ which arise distal to it. In fact, all parts of the nerve may contribute to the resulting sensation.

Another difference between post-ischæmic paræsthesiæ and centripetal anæsthesia is important. Contrary to the accounts of many writers, the area in which the paræsthesiæ are felt does not increase in a strictly centripetal fashion as the duration of ischæmia is increased. In short experiments on the upper limb, for example, tingling or pricking is not confined to the finger-tips, but may involve any part of the palmar surface of the hand or fingers. Even in very brief experiments resulting in fleeting and barely perceptible paræsthesiæ, the sensations are usually felt scattered all over the median and ulnar areas. In longer experiments the sensations are increased in intensity, but they still remain confined to the same areas ; it is only after prolonged arrest that the paræsthesiæ may spread to involve the forearm. It is difficult to account for this relatively constant distribution of the paræsthesiæ by a greater sensitivity of longer nerve fibres to a return of the circulation, as suggested by Lewis, Pickering, and Rothschild. Further, such an hypothesis does not account for two conflicting facts already commented on : first, that release of the

* Weddell and Sinclair were unable to induce " release pricking " in two amputation cases. One possible reason for the failure of some amputation cases to exhibit post-ischæmic paræsthesiæ has already been given ; thus, out of seven such cases examined by us, post-ischæmic pricking was obtained in two.

circulation to the whole limb does not normally produce paræsthesiæ in areas of the forearm supplied by long cutaneous nerves, and secondly, that release of very short lengths of median or ulnar nerves results in paræsthesiæ in the areas supplied by them. These apparently incompatible results may perhaps be best explained on the basis of a peculiar sensitivity of the larger peripheral nerves (e.g. median, ulnar, radial) to a return of the circulation. Some property of a large nerve as such, appears to determine the reactions of its component nerve fibres. Paræsthesiæ are felt in the palm, not because the sensory fibres leading from the palm are long, but rather because they are contained in one of the largest nerves in the arm. Why the large nerves should react so characteristically to arrest and return of the circulation is not at present clear.

Results already given suggest that each form of paræsthesia is related to a particular form of peripheral sensation ; tingling to the sensation of touch, pricking to the sensation of pressure, and pseudo-cramp to the sense of movement and position. The paræsthesiæ may be modified, each to a different extent, by changes in the temperature of the whole limb, by repeated circulatory arrest, and occasionally by deliberate partial nerve block, which procedures are known to affect the conduction in sensory fibres to varying degrees. There is some physiological basis, then, for the supposition that tingling, pricking, and pseudo-cramp are distinct phenomena associated with different sensory nerve fibres. The prominence of pseudo-cramp after release of the radial nerve may be due to the presence in this nerve of a high proportion of fibres subserving position sense, and a correspondingly small number of cutaneous afferent fibres. Several authors have noted the unpleasant and painful character of post-ischæmic paræsthesiæ, and particularly of the pricking element ; a few, Zotterman, Kugelberg, and Weddell and Sinclair, have been led to believe that this sensation results from impulses travelling in pain-conducting nerve fibres. But the fact that all paræsthesiæ may still be induced when the pain, thermal, and sympathetic pathways have been blocked, excludes the possibility of their origin or conduction in any of these pathways. There seems, in fact, to be no paræsthesia associated with pain sense in the post-ischæmic period. Nor is there any evidence to suggest activity of the sympathetic nerve fibres ; vasoconstriction, sweating, and erection of the hairs have not been observed after release of the circulation. It is to be noted that sympathetic nerve fibres, and those concerned in the conduction of impulses felt as pain, are both of small diameter and non-medullated, and are known to be relatively resistant to the effects of asphyxia.

In this study no attempt has been made to account for the mechanism underlying the production of post-ischæmic paræsthesiæ ; investigations relating to this problem are still being conducted. That the effect is primarily a vascular one has been suggested by Lewis and his associates, and has been confirmed in experiments recorded here. It has been shown that an adequate period of ischæmia must be followed by an adequate period of normal circulation in a nerve, before this nerve becomes the seat of changes felt as paræsthesiæ.

Although these changes are apparently initiated within a few seconds of release of the circulation, they progress relatively slowly, for there is a striking and constant delay before the paræsthesiæ actually do begin. Kugelberg's studies show that the excitability of human motor nerves to electrical stimuli is greatly increased at about the time when paræsthesiæ are at their height ; it is likely that the appearance of spontaneous impulses felt as paræsthesiæ is directly related to a similar increase in excitability in the sensory nerves.

A clear distinction should be drawn between the delay before the appearance of paræsthesiæ, and the time taken for anæsthesia to recover, after the return of the circulation to an ischæmic limb. The two events are independent. In the first place, the usual delay which precedes the paræsthesiæ can be observed after periods of ischæmia so brief that peripheral sensation has never been demonstrably affected. Further, in experiments of longer duration, sensation in the territory of a given nerve may fully recover many seconds before the paræsthesiæ are first felt in that area. The nerve regains its ability to conduct before it enters the phase of increased excitability. For many hours after this phase has passed and paræsthesiæ have ceased, the nerve still remains in an abnormal state, although sensation in its territory is apparently perfectly normal. During this period, as Lewis, Pickering, and Rothschild have described, further arrest of the circulation leads to the unusually early onset of anæsthesiæ and paralysis ; but it may also be observed that ischæmic and post-ischæmic paræsthesiæ are much reduced in severity. We have already pointed out that diminution of the ischæmic paræsthesia is a most sensitive indicator of these residual effects in a limb ; by noting its absence, we have found on many occasions that the effect of compression of the arm for thirty minutes lasts fully twenty-four hours. The nature of this remarkably persistent change in the nerve is at present unknown.

Summary

Certain forms of paræsthesiæ felt on release of the circulation to an ischæmic limb have been investigated.

The various paræsthesiæ are defined and described, and methods of producing them separately are given. An account is given of the more important factors modifying the paræsthesiæ.

Evidence is presented which shows that the nerve impulses felt as paræsthesiæ arise in the nerves recovering from ischæmia, and not in the end-organs.

It is shown that the nerve fibres concerned are those which normally subserve the sensations of touch, pressure, and movement. Pain, temperature, and sympathetic fibres play no part.

Evidence is given which shows that the paræsthesiæ are conducted in the posterior columns of the cord, and not in the antero-lateral columns.

We take this opportunity of thanking the physicians of the National Hospital, Queen Square, who put their cases at our disposal. We are particularly grateful also to Dr. W. R. Trotter for his help and advice throughout this investigation and to Dr. E. A. Carmichael for his help and criticism in writing the paper.

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SOME EXPERIMENTAL AND CLINICAL OBSERVATIONS ON THE ANTICONVULSIVE ACTION OF PARALDEHYDE*

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In the practice of neurosurgical operations the convulsions occasionally elicited during cortical manipulations or produced by electrical stimulations may sometimes be difficult to control, and may give rise in some cases to dangerous convulsive states that may even end fatally. Barbiturates and other common drugs may fail to stop such convulsions quickly, as we have observed in some of our cases.

We have recently tried paraldehyde by intravenous injection in the treatment of such convulsive states, and the good results obtained have been the basis for an experimental and clinical study of this drug. In the literature we have found that Cervello (1884) was the first to use paraldehyde by mouth and rectum for narcosis. Nitzescu and Iacobovici (1934) recommended paraldehyde by intravenous injection (0·15 to 0·2 c.cm. per kg.) as a basal anæsthetic before the administration of ether. Wechsler (1940) has also successfully employed the slow intravenous injection of 1 c.cm. of paraldehyde for the treatment of status epilepticus.

Toxicity

Paraldehyde has relatively little toxicity by the intravenous route. Experimentally 0·5 c.cm. per kg. in cats produces only a small and transitory reduction of the blood pressure and respiration. With smaller doses (0·1 to 0·2 c.cm. per kg.) injected into rabbits, cats, and dogs there are no changes in respiration or circulation.

In human beings the intravenous injection of 1 to 3 c.cm. does not alter the pulse, blood pressure, or consciousness. There may be a slight fall in blood pressure lasting a few minutes. Frequently there is intense coughing for two to five minutes after the injection, with individual variations and caused by the irritation of the bronchial tree due to the partial elimination of the paraldehyde through the lungs. Usually there is also a stimulation of the respiration with hyperpnœa.

Higher doses of 6 c.cm. of intravenous paraldehyde in adults (about 0·1 c.cm. per kg.) produce a narcotic effect with some diminution of consciousness and a tendency to sleep, although the subject will still react to painful stimuli. There is also a slight fall in blood pressure. With bigger doses (9 to 12 c.cm. in adults) the narcotic action is more marked and usually the patients fall asleep at the end of the injection. The cough does not appear, the blood pressure falls slightly, and there is an increase in the rhythm and amplitude of the respirations.

Action on the Motor Responses of the Cerebral Cortex

In cats under dial anæsthesia the motor area was stimulated and the contractions of the contralateral tibialis anterior muscle were isometrically recorded. Condenser discharges of 10 m.sec. duration and with a frequency of 50 per second were applied through a bipolar electrode during periods of 5 seconds.

The same type of stimulation was employed in five patients submitted to neurosurgical operations, where the stimulation was necessary because of epileptic disorders or for delimitation of the motor area in cortical removals for athethosis.

Paraldehyde in small doses (0·05 to 0·1 c.cm. in cats and 1 to 3 c.cm. in men) produced a clear diminution of the motor responses of the cortex, with great elevation of the threshold of stimulation and even a complete abolition of the responses. Experimentally we have determined that the depressive action on the motor cortex lasted for 20 to 30 minutes, and afterwards the excitability recovered slowly although the diminution persisted for some time.

In some clinical cases the cortical stimulation produced a convulsive attack and the injection of paraldehyde stopped the convulsions immediately. Further stimulations were completely negative, and only with intense stimuli some slight clonic discharges were obtained in one epileptic patient.

Action on the Electrical Activity of the Cerebral Cortex

Cats under nembutal were used for recording the electrical activity of the cortex with electrodes inserted in the skull and in contact with the dura. A Grass electroencephalograph of four channels was employed for recording.

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The spontaneous activity of the cortex typical of the cat under nembutal with frequencies of 4 to 12 per second and 50 to 200 microvolts was not apparently modified by small doses of paraldehyde (0·05 c.cm. per kg.). Greater doses (0·1 c.cm. per kg.) produce, however, an obvious diminution of the spontaneous cortical activity that appears at 20 or 30 seconds from the injection time (Fig. 1). This effect lasts about 15 to 20 minutes, followed by slow recovery. Using higher amounts of paraldehyde (0·15 to 0·2 c.cm. per kg.) the complete elimination of activity is very striking, as we shall see later (Fig. 3).

Paraldehyde also stops the convulsive activity of the cortex elicited by intravenous injection of leptazol (300 to 600 mg.). These convulsive discharges of very large voltage and high frequency appear a few seconds after leptazol injection, and paraldehyde abolishes such activity immediately (Fig. 2). The convulsive discharges may continue for several minutes in the control experiments. Sometimes paraldehyde in bigger doses (0·2 c.cm. per kg.) not only stops the convulsive activity, but may also abolish completely all signs of electrical activity in the brain (Fig. 3). This complete depression of the cortex lasted two minutes and afterwards some isolated discharges of spontaneous waves reappear, but it takes about 15 minutes before a marked recovery is noticed.

In several epileptic patients in the course of routine electroencephalographic studies, paraldehyde was injected intravenously in small doses of 2 to 3 c.cm. In some cases there was no noticeable change in the activity of the electroencephalogram, probably because of the small amount injected. But even these doses produced in two cases a diminution of the abnormal activity. Further studies are still necessary, injecting larger amounts of paraldehyde.

Anticonvulsive Action

The anticonvulsive action of paraldehyde has been studied experimentally in rabbits and cats.

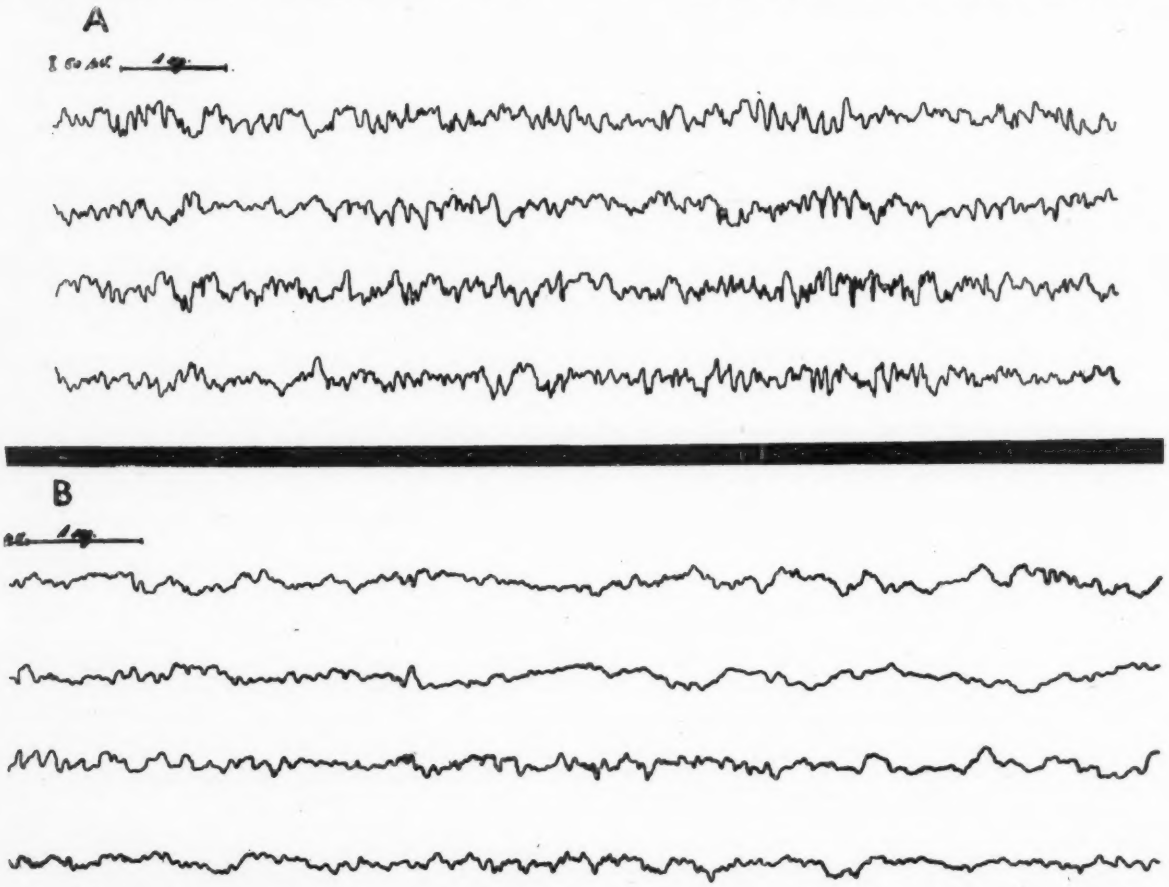


FIG. 1.—Electrical activity of a cat's cerebral cortex under Nembutal, before (A) and after (B) a small dose of paraldehyde (0·1 c.cm. per kg.).

This drug, in doses of 0·1 to 0·2 c.cm., is very effective in preventing and immediately stopping the very severe and lasting convulsions produced by large doses of leptazol and strychnine. The convulsions elicited by local applications of strychnine on the motor cortex of the cat under nembutal anæsthesia are also stopped to a striking degree by paraldehyde (Fig. 4). An animal injected with paraldehyde is completely protected even against very large doses of several mg. of strychnine. The anticonvulsive action appears also in the decerebrate and spinal preparation of the cat.

Clinically we have also confirmed the intense anticonvulsive action of paraldehyde in several cases of epileptic attacks during or after neurosurgical operations. Even in cases under combined rectal avertin and intravenous pentothal anæsthesia we have seen convulsive fits during removal of scars or other cortical lesions that have quickly stopped with doses of 2 to 4 c.cm. of intravenous paraldehyde. Serious and prolonged status epilepticus has also been controlled by an injection of paraldehyde that sometimes had to be repeated once or even twice in the course of several hours. We have never seen any complications or secondary effects after the use of paraldehyde.

Other Pharmacological Actions

The action of paraldehyde has also been studied on some pharmacological preparations. On the nerve and muscle preparation of the rat's diaphragm (Bülbring, 1946) this substance reduces the muscular responses to the electrical stimulation of the phrenic nerve (Fig. 5). The same depression has been observed on the nerve and muscle preparation of the sciatic nerve of the cat (Fig. 6). In the perfusion of the superior cervical sympathetic ganglion of the cat with the technique of Kibjakow (1933), modified by Feldberg and Gaddum (1934), the paraldehyde produces also a marked depression on the ganglionic synapse (Fig. 7).

Discussion

Our experimental and clinical observations on the effects of paraldehyde demonstrate very clearly the great depressive action of this drug on different

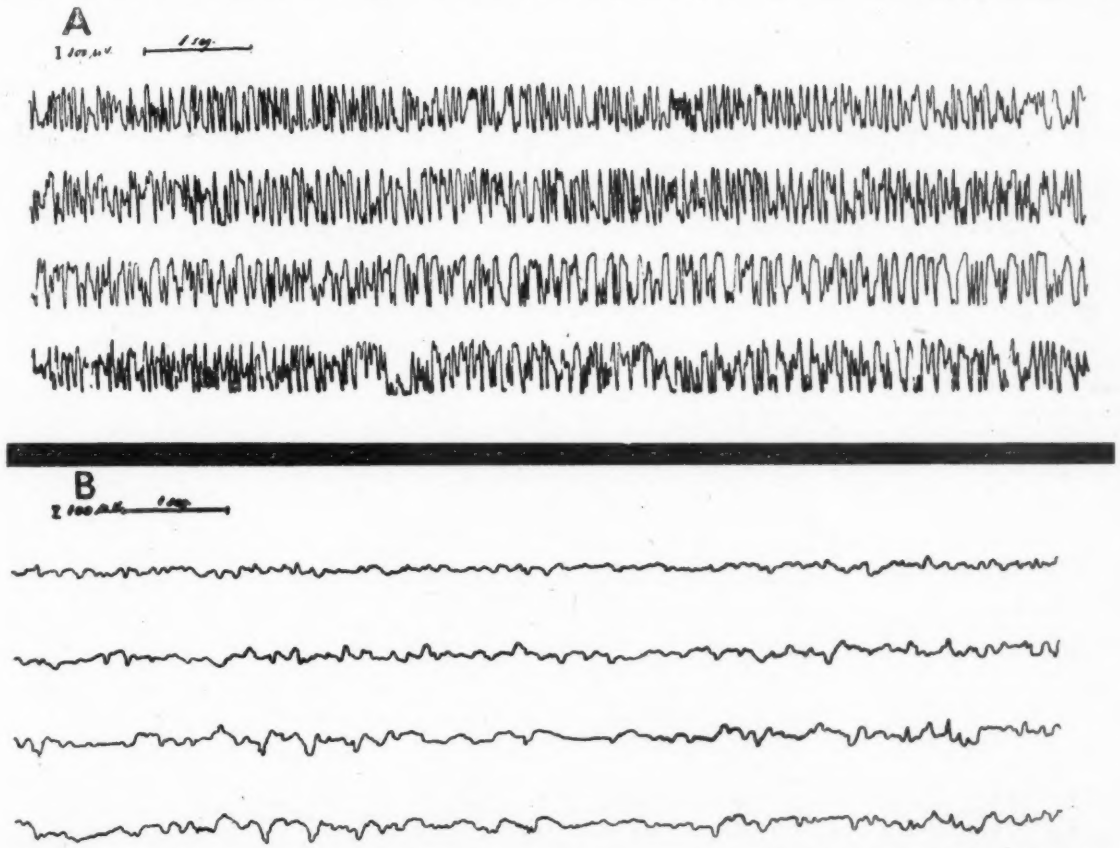


FIG. 2.—Convulsive activity of the cat's cortex after leptazol (A) abolished by paraldehyde (B).

levels of the nervous system—peripheral, spinal, and cerebral. The action seems, however, more marked on the cerebral cortex, where paraldehyde can completely eliminate for several minutes all signs of electrical activity in the cat.

The mechanism of action of this substance is unknown to us, and in some preliminary experiments using the preparations of guinea-pig intestine and the rectus muscle of the frog we have seen that paraldehyde does not antagonize the action of acetylcholine.

From a theoretical point of view, the great anticonvulsive action of paraldehyde has some interest because of the similarity of this substance to other organic aldehydes that are normally formed in the complicated steps of the hydrocarbonate metabolism. Perhaps we may presume that paraldehyde acts something like other substances (glucose, carbon dioxide, pyruvic acid, etc.) that are considered as "physiological" anticonvulsants and regulators of the neuronal discharges. We hope to extend this line of investigation, comparing the anticonvulsive action of paraldehyde with other organic compounds and especially those related to the carbohydrate metabolism, although it is well known that the majority of the compounds that take a part in such metabolism are very unstable.

From a practical standpoint we believe that intravenous paraldehyde is actually the best agent that we have to stop an epileptic discharge immediately. It can also be used as a prophylactic drug against operative convulsions in cortical operations on epileptic patients. The small toxicity of this substance is a very important factor if a repetition of the injection is necessary. We recommend as a first dose about 0·05 c.cm. to 0·1 c.cm. per kg., and if the convulsions reappear the injection may be repeated one or two hours later. Although, as we have seen in our experimental studies, the marked action lasts only fifteen to thirty minutes, it is only necessary to inject the paraldehyde once to break the epileptic state and usually the convulsions do

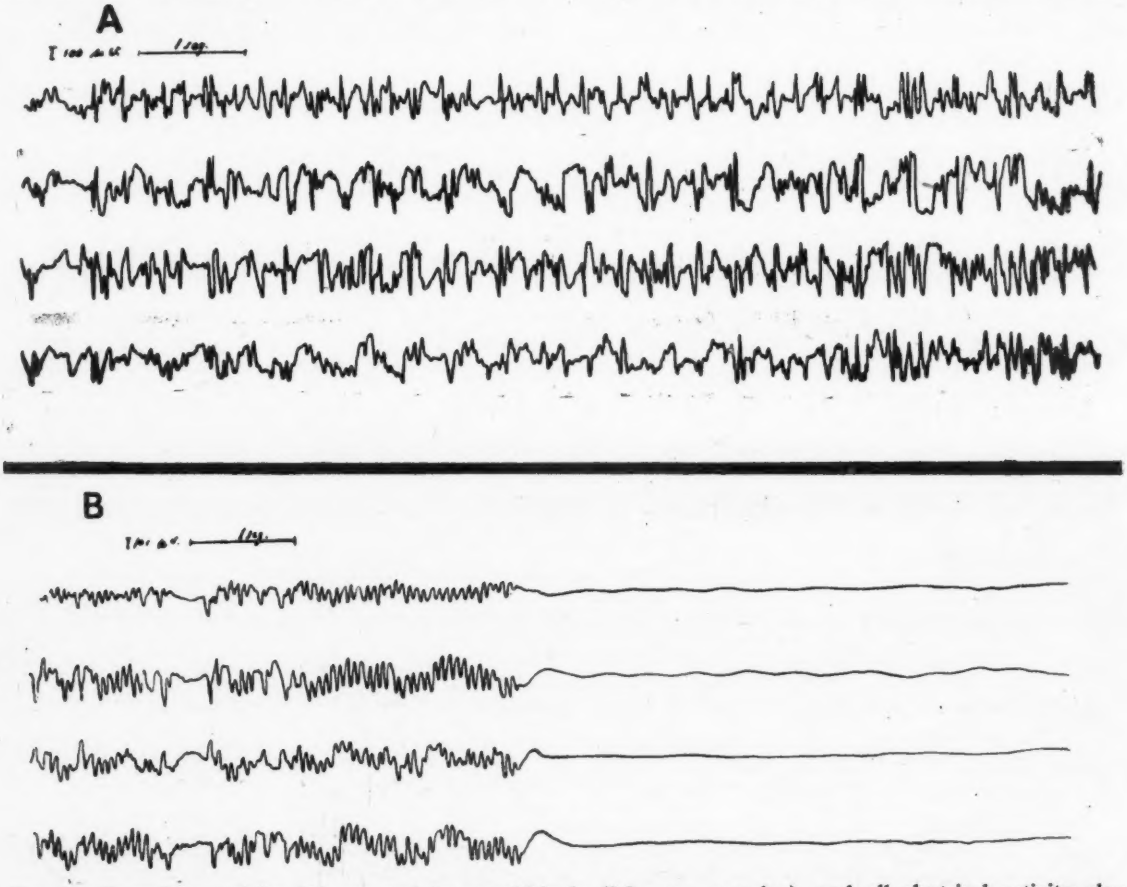
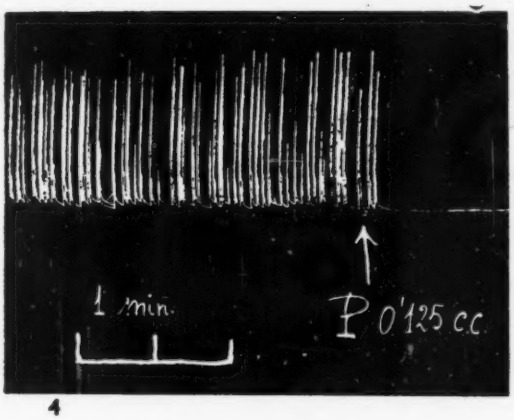


FIG. 3.—Convulsive activity (A) arrested by paraldehyde (0·2 c.cm. per kg.), and all electrical activity also abolished (B).



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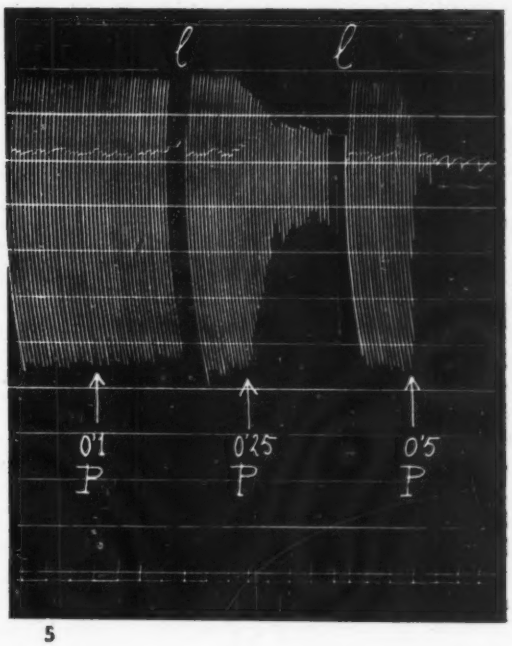

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FIG. 4.—Electrocorticogram to illustrate the abolition of strychnine convulsions after the intravenous injection of paraldehyde at P.

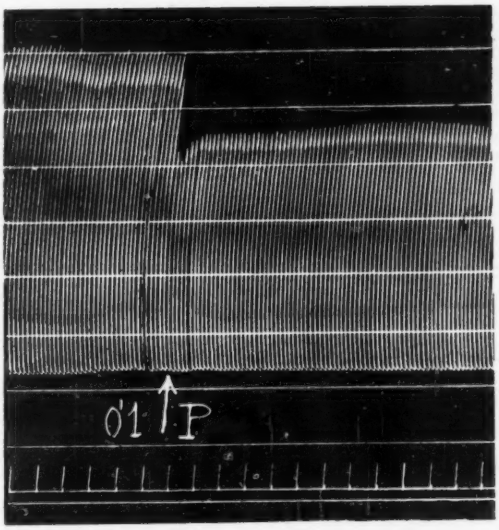

FIG. 5.—The effect of paraldehyde in reducing the muscular response of the isolated diaphragm of the rat to electrical stimulation of the phrenic nerve.

FIG. 6.—Contractions of the gastrocnemius muscle of the cat (under chloralose) elicited by stimulation of the sciatic nerve. Depression of contractions following the administration of paraldehyde at P.

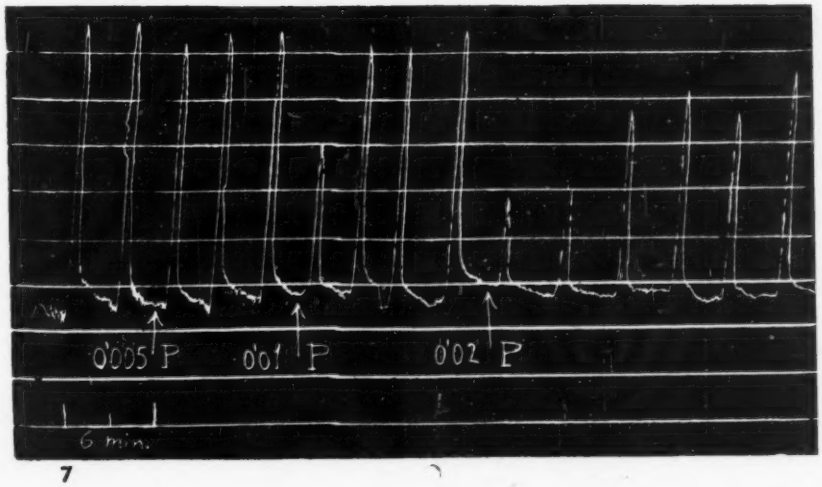

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FIG. 7.—Superior cervical ganglion of the cat isolated and perfused with Locke solution. Stimulation of preganglionic fibres causing contraction of the nictitating membrane of the cat's eye. Depression of transmission of impulses by injection of paraldehyde into the fluid perfusing the ganglion at P.

not recur. An annoying side effect is the cough that follows the injection and that may last several minutes with great intensity in some individuals.

Summary

Paraldehyde is a substance with little toxicity that can be injected intravenously in doses of up to 0·2 c.cm. per kg. without any ill-effects. Large doses have a narcotic action.

The motor responses of the cerebral cortex of the cat and human beings are greatly reduced or abolished by small doses of paraldehyde. The convulsive attacks produced in the course of neurosurgical operations by cortical stimulation are immediately stopped by paraldehyde.

Paraldehyde reduces or abolish for some minutes the spontaneous cortical activity of the cat according to the dose employed. Convulsive discharges of the cortex elicited by leptazol disappear immediately with the injection of paraldehyde.

The anticonvulsive action is also very striking in animals injected with different convulsant drugs. A dose of paraldehyde protects an animal against large doses of strychnine and leptazol. The anticonvulsive action appears also in the decerebrate and spinal preparations. Clinically, paraldehyde has been used in many cases to stop operative or postoperative convulsions that in some cases may reach serious proportions.

The depressing action of paraldehyde has also been demonstrated on the peripheral neuromuscular junctions and on the ganglion synapses, although the action is more marked on the cerebral cortex.

The theoretical implications and mechanism of action of paraldehyde are briefly discussed. This substance is recommended in doses of 0·05 to 0·1 c.cm. per kg. intravenously as the best agent that we actually have to break and stop a convulsive discharge. The dose may be repeated if necessary.

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SYNCOPE AND SEIZURES*

BY

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Introduction

Syncope is a clinical syndrome usually caused by vasomotor, reflex, or psychogenic disturbances. Various authors have emphasized that syncope or fainting is sometimes difficult to distinguish from epilepsy (Weiss, 1935, 1942; Rossen, 1947), and it has long been suggested that in some instances (Gowers, 1907; Wilson, 1928; Baxter and others, 1944) syncopal attacks might be the manifestation of an epileptic disorder. In patients with syncope the electro-encephalogram between attacks is normal (Levin and others, 1945; Sugar, 1945), although the period of unconsciousness is accompanied by high-voltage slow waves which are reversible (Forster and others, 1942; Engel, 1945). In contrast, 90 to 95 per cent. of patients with clinical epilepsy have an abnormal inter-seizure record (Jasper and Kershman, 1941, 1944; Gibbs and others, 1943).

The present report deals with a group of 114 patients who had a history of syncopal attacks or similar episodes without loss of consciousness, and all of them had abnormal electro-encephalograms between attacks. None of these patients had a definite convulsive seizure. The problems of diagnosis and relation to clinical epilepsy will be discussed.

Material and Methods

Most of these 114 patients were members of the Canadian Armed Services, and 85 per cent. were between 18 and 30 years of age. Over 90 per cent. were men, and those with any evidence of other organic disease were excluded. Patients who had a history of at least one convulsive seizure were also excluded and are described in a separate study (Kershman and Elvidge, 1948).

The method of electro-encephalogram (E.E.G.) examination was essentially the same as described previously (Jasper, Kershman, and Elvidge, 1940; Jasper and Kershman, 1941). With each patient a minimum total time of thirty minutes was recorded, various parts of the head being symmetrically explored with scalp-to-scalp and scalp-to-ear records. Hyperventilation was carried out for three minutes and the record continued for two minutes after. If the record was on the borderline of normal, it was repeated after hydration and pitressin, using the regime outlined by Penfield and Erickson (1941). In patients who had a history that alcohol was a precipitating factor in the attacks, the following was frequently carried out in addition to the standard E.E.G. The patient was given one ounce of whisky in a glass of sweetened fruit juice, and this was repeated after one and two hours. An E.E.G. was started within half an hour after the last drink.

The criteria for abnormality in the E.E.G record are based on the author's experience with many thousands of normal and abnormal tracings in a wide variety of neurological and psychiatric conditions and in normal persons.

Abnormalities were classified as focal, diffuse, or bilaterally synchronous in accordance with the scheme previously described (Jasper and Kershman, 1941). This is preferred because it provides a better understanding of the nature of the abnormal discharges, but it does not differ as far as normal and abnormal criteria are concerned from other classifications, such as that proposed by Gibbs and others (1943). Frequencies slower than 7·5 per second and faster than 12·5 per second were considered abnormal if their amplitude was larger than the background alpha.

Results

Clinically the 114 patients could be divided into two groups: (*a*) in 92 patients there was a history of at least one attack in which loss of consciousness occurred; (*b*) in 22 patients there was no history of loss of consciousness.

In both groups the distribution of the various types of E.E.G. abnormality was surprisingly similar.

A. Spells with Loss of Consciousness.—In this group of ninety-two patients who had syncopal spells the commonest E.E.G. abnormality was a diffuse dysrhythmia which occurred in 65 per cent. (Table I). This consisted of mixed random slow

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waves usually varying between 2 to 6 per second, or mixed fast and slow waves, with fast frequencies occasionally predominating. Characteristically in this group there was almost a complete absence of normal alpha frequencies (7·5 to 12·5 per second).

Bilaterally synchronous abnormalities were present in 29 per cent., the commonest form (17 per cent.) being 6 per second rhythms and 4, 5, and 7 per second variants. Typical 3 per second slow wave and spike discharges were infrequent, being seen in only 5·5 per cent. and variants of this activity occurred in 6·5 per cent.

TABLE I

SYNCOPAL SPELLS WITH LOSS OF CONSCIOUSNESS

Type of E.E.G. abnormality	No.	%
Diffuse dysrhythmia	60	65
Bilaterally synchronous disturbances	26	29
3/sec. wave and spike ..	5	5·5
3/sec. variants	6	6·5
6/sec. rhythms and variants	15	17
Focal abnormality	6	6
Total ..	92	100

In 6 per cent. the pathological E.E.G. activity could be localized to a discrete cortical area, and in every instance it was in the temporal region as far as could be determined from scalp electrodes.

EXAMPLES

1. *F.R.B. Syncopal Spells with Diffuse Slow Dysrhythmia.*—This patient, a sergeant-navigator on operational duty in England, was repatriated because of two spells of unconsciousness in three years. The first occurred during training after he had been working all night. Shortly after he had his breakfast, while reading the newspaper, he suddenly felt a choking sensation, stood up and fell unconscious. He had urinary incontinence and recovered about fifteen minutes later feeling weak and dizzy. His mother, who witnessed the attack, said that no convulsive movements occurred. The second attack happened late at night while reading. His eyes felt tired and he recalled some twitching of his lips. His air-crew comrades who saw the spell did not notice any convulsive movements but again there was urinary incontinence. There was no history of childhood seizures, no family history of epilepsy or fainting, and no history of head injury.

The *E.E.G.* (Fig. 1) showed diffuse slow irregularity in all head regions with no appreciable alpha. There was a definite increase in voltage and amount of abnormality with hydration. It should be emphasized that in this and subsequent examples, the E.E.G. records were taken from interseizure periods and no patient had a record during one of the actual spells described.

2. *N.W.P. Fainting Spells with Mixed Fast and Slow Dysrhythmia.*—This patient was a 29-year-old airframe mechanic referred because of fainting spells. There were about six in the past year and a half, and usually they came on when he was tired or after standing a long time at roll call, but they also occurred without any obvious cause. He gave a history of fainting easily when he cut himself and bled even slightly, or when he saw anybody else hurt. He complained of dizziness on bending over, excessive sweating, headaches, dizzy spells, blurring of vision, and heartburn with gastric pain for the past three years, usually after meals. A barium series of the gastro-intestinal tract was normal. His pulse was rapid and there was a coarse tremor of his outstretched hands. A diagnosis of anxiety neurosis had been made.

The *E.E.G.* (Fig. 2) showed mixed fast and slow waves, very little alpha, and a sharp increase in the abnormal activity with hyperventilation.

Comment.—A history of vasomotor instability, nervousness, postural dizziness, and frank anxiety states was quite common in patients of this group with syncope and diffuse dysrhythmia. Often the spells occurred only under special conditions of stress and fatigue, but in other cases there were no

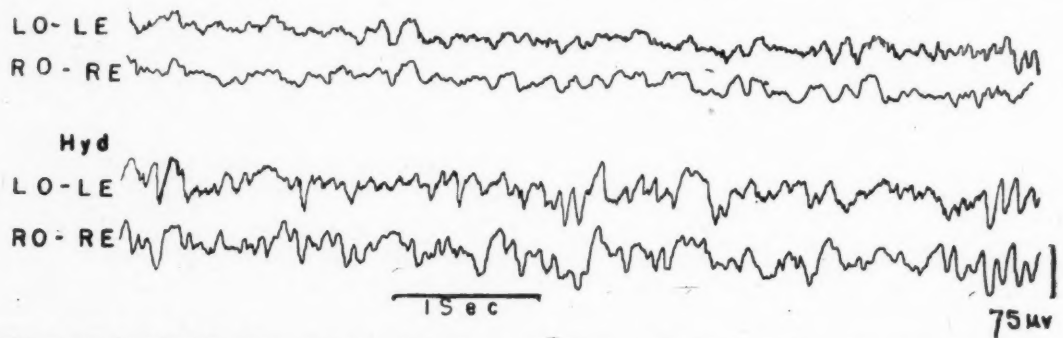


FIG. 1.—Patient F.R.B. Syncope with diffuse slow dysrhythmia. LO–LE is the record from the left occiput to the left ear lobe. RO–RE is the record from the right occiput to the right ear lobe. The first two lines show the generalized slow irregularity in the resting record. The lower two lines show the increase in abnormality after hydration.

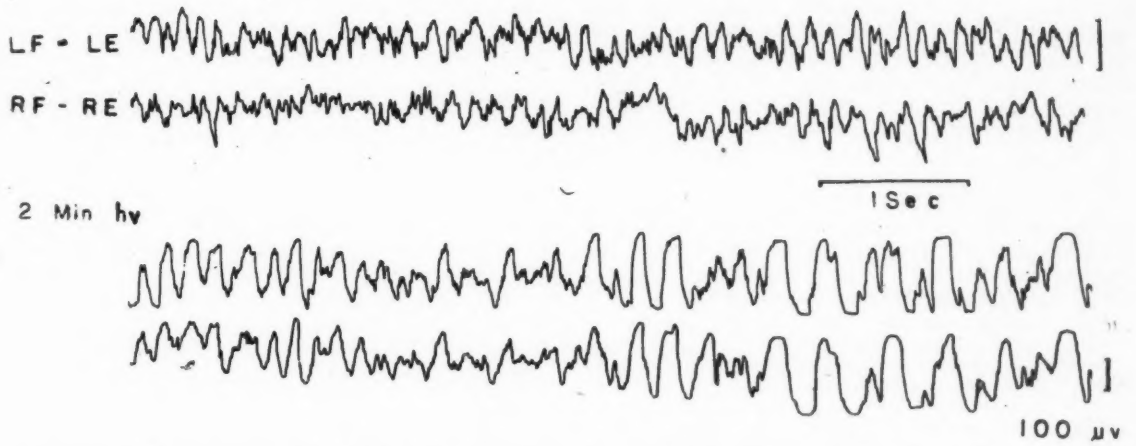


FIG. 2.—Patient N.W.P. Fainting spells with mixed fast and slow dysrhythmia. LF–LE is the E.E.G. from the left frontal region to the left ear lobe ; RF–RE is the homologous record from the right side. The lower two lines show the marked increase in voltage and amount of abnormality with rhythmic bisynchronous tendencies after two minutes hyperventilation.

obvious precipitating factors, and there might be a vague history of fainting spells in childhood. In many patients the syncope was preceded by a brief aura of "dizziness," "blackness," "blurring of vision," or "billiousness," and these complaints sometimes occurred without loss of consciousness.

3. *G.E.S. Syncope with Bilaterally Synchronous 6 per second Waves.*—This patient was a 20-year-old airman referred because of a single fainting attack which occurred in the dentist's chair after he had had his tooth drilled. He stated that he had always been fearful of the dentist's drill since early childhood. There was a history of frequent head injuries and one maternal cousin had a history of epilepsy.

The *E.E.G.* (Fig. 3) was characterized by very frequent bursts of rhythmic 6 per second discharges. The amount and voltage increased with hyperventilation.

Comment.—Patients in this group with syncope and 6 per second abnormalities also frequently had precipitating factors of an emotional or painful nature. They often complained of dizziness, or "fogginess inside their head," as an aura or occurring without syncope.

4. *R.A.C. Fainting Spell with 3 per second Abnormalities.*—This airman, aged 21, was referred because of a single fainting spell which occurred after he had given blood at a Red Cross donor clinic. Loss of consciousness lasted several minutes and was not accompanied by convulsive movements.

The *E.E.G.* at rest was normal (Fig. 4). After one minute of hyperventilation, paroxysmal bisynchronous 2 to 3 per second waves appeared which quickly formed rhythmic patterns. Some of this abnormality was still present one and a half minutes after the end of overbreathing. Hyperventilation was repeated after 75 g. of glucose and showed the same effect.

Comment.—Patients in this group with 3 per second abnormalities did not usually have the auras, vasomotor complaints, or symptoms of anxiety commonly seen in the patients with diffuse dysrhythmias and those with 6 per second abnormality.

There were six patients with syncopal spells who had a focal abnormality. In all of them, slow waves were present in and around the right temporal region.

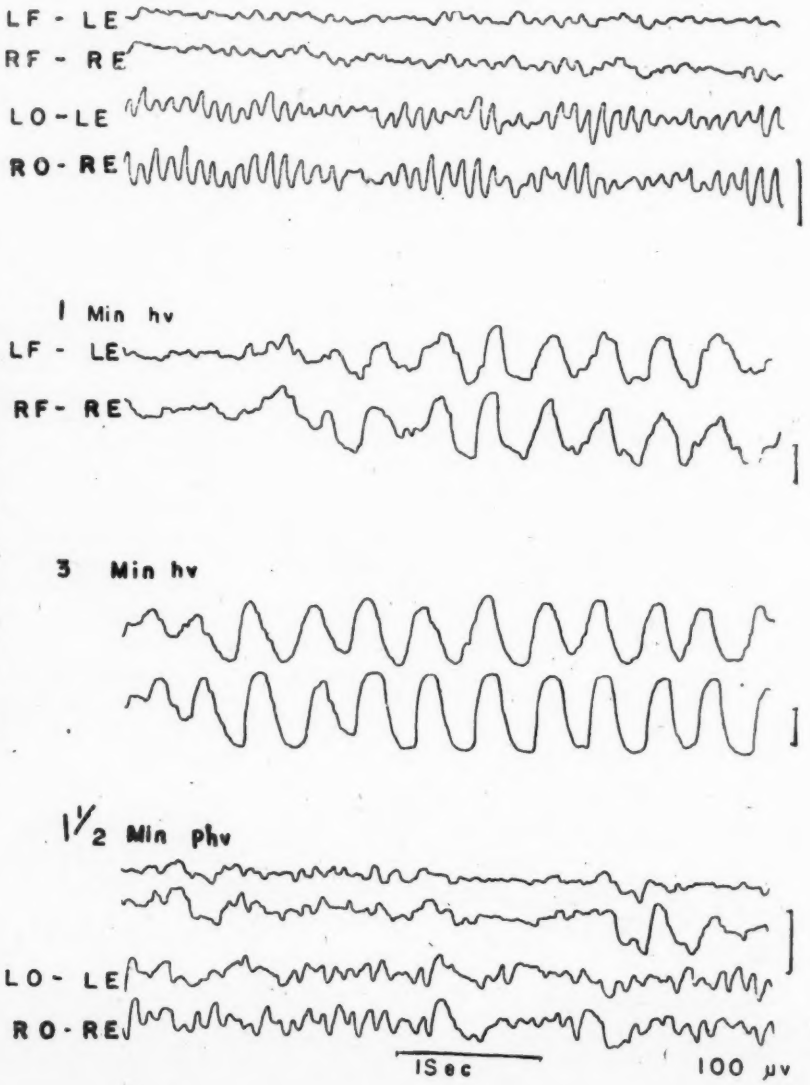
FIG. 3.—Patient G.E.S. Syncope with bilaterally synchronous paroxysmal 6 per second waves. LF–LE is the record from the left frontal region to the left ear lobe ; RF–RE is the homologous record from the right side.

5. *G.R.C. Focal Right Temporal Abnormality.*—This patient was a 24-year-old Flying Officer who was sent home from active duty in England because of three spells, all occurring during flying. In one of them, he suddenly fainted after complaining of a midfrontal headache for about half an hour. In the other two, he had the same headache followed by what was described as bizarre behaviour lasting for two hours. He had no recollection of these episodes other than the headache. Because of the spells, an R.A.F. psychiatrist in England repatriated him with the diagnosis of "constitutional neurosis."

The *E.E.G.* (Fig. 5) showed a clear focus of slow wave activity localized to the right temporal region.

Comment.—Periods of mental confusion and bizarre behaviour were frequent in these patients and it seems clear from the history and the E.E.G. that these were probably ictal automatisms, originating from the temporal region.

B. Spells Without Loss of Consciousness.—In twenty-two patients, there were *episodic disturbances* which were never accompanied by either loss of consciousness or a convulsion. These episodes were similar to the auras seen in many of the ninety-two patients described above with syncope, and often occurred without loss of consciousness in the same patients. Engel (1945) and Stead (1947) have described similar phenomena as "fainting reactions." There were periods of sudden transient dizziness, blurring of vision,



G . 4.—Patient R.A.C. Fainting spell with bilaterally synchronous 3 per second waves. LF and RF are the left and right frontal regions, LO and RO are the left and right occipital regions; LE and RE refer to the left and right ear lobes. The upper four lines are the resting record. This is followed by strips at one minute of hyperventilation and at three minutes of hyperventilation showing pathological discharges of bilaterally synchronous high voltage 2 to 3 per second rhythmic waves. Slow irregular waves were still present one and a half minutes after the end of overbreathing as shown in the lower four lines.

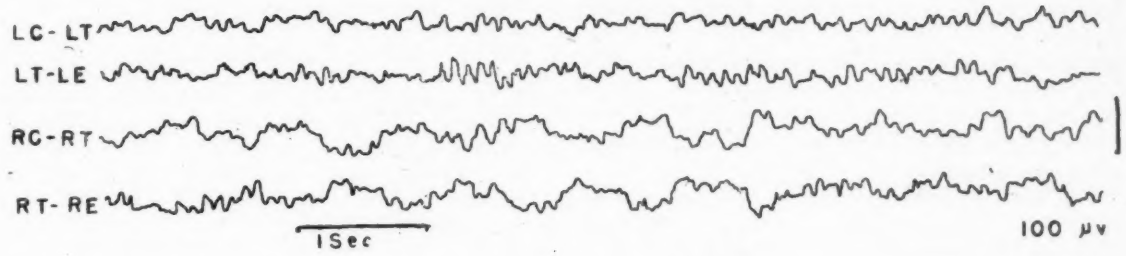


FIG. 5.—Patient G.R.C. Focal right temporal lobe discharges. LC–LT is the E.E.G. from the left central to the left temporal region; LT–LE is left temporal to the left ear lobe; RC–RT and RT–RE are the homologous regions on the right side and show slow waves at 1 to 2 per second localized to the right temporal region. The spells consisted of headache and automatisms, and on one occasion there was loss of consciousness.

sometimes accompanied by abdominal sensations (similar to the patients described by Moore (1948)), feelings of weakness without loss of consciousness, or "blackout." The term "blackout" is a by-product of the last war and many patients used it to describe a variety of different subjective feelings. It should be emphasized that only a few of the very many who described this symptom had an abnormal E.E.G. and came into this group under discussion.

Just as in the group with loss of consciousness, the commonest E.E.G. abnormality was a diffuse dysrhythmia, occurring in the same proportion, or 64 per cent. (Table 2). Bilaterally synchronous abnormalities were present in 36 per cent., the commonest (31 per cent.) being bisynchronous 6 per second rhythms and its variants. There were no typical 3 per second wave and spike patterns, and only one patient showed a variant of this abnormality.

EXAMPLES

6. *B.P.O'C. Spells with Diffuse Dysrhythmia.*—This airman aged 19 was referred because of spells of dizziness, weakness, nausea, sweating, and "things go black sometimes." These spells occurred about once a month for the past three years and lasted from a few seconds to a few minutes. There was a family history of instability and the patient showed maladjustment in his childhood and work history. A tentative diagnosis of "anxiety neurosis with petit mal" was made.

The *E.E.G.* (Fig. 6) showed a poorly organized background containing very little normal alpha and there was slow activity with waves at 2 to 6 per second showing only occasional rhythmic tendencies.

7. *A.G. Spells with Bisynchronous 6 per second Waves.*—This patient, aged 26, was referred for spells of giddiness with sweating which came on every two to three weeks for the past few years, lasting about one to two minutes. At times, the spells were accompanied by what he described as "blackouts" in which he fell to the ground, but careful questioning showed that he did not lose consciousness. There was a history of emotional instability in childhood and periods of irritability at the time of referral, as well as frequent frontal and generalized headaches.

E.E.G. (Fig. 7). The resting record showed a poorly organized alpha with low voltage 6 per second paroxysmal waves. The latter were increased with hyperventilation and persisted quite a long time after.

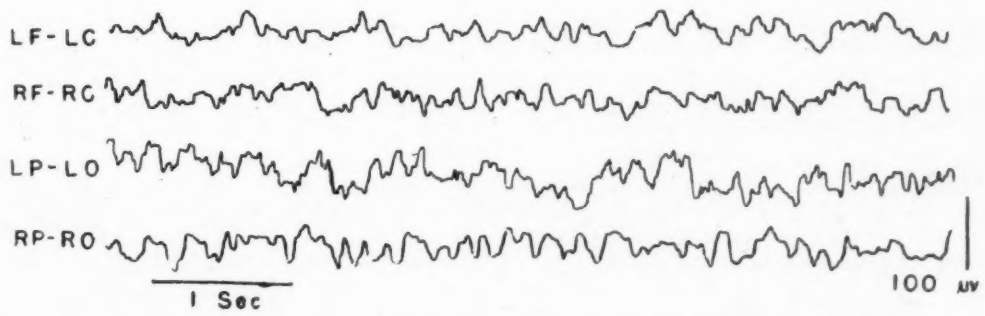


FIG. 6.—Patient B.P.O'C. Spells of weakness, nausea and dizziness with diffuse dysrhythmia. LF–LC is the E.E.G. from the left frontal to left central regions, RF–RC from the right homologous area, LP–LO from the left parietal to left occipital regions and RP–RO from the right homologous region.

Comment.—The predominant symptoms of the patients in this group were dizziness, sweating, nausea, and weakness which came on suddenly and usually without any obvious cause. These might be described as periodic episodes of vasomotor hyperactivity, and it was often accompanied by subjective anxiety.

The next example illustrates that in one patient of this group a generalized convulsion could be precipitated under hydration although it had never occurred spontaneously.

TABLE II

EPISODIC DISTURBANCES WITHOUT LOSS OF CONSCIOUSNESS

Type of E.E.G. abnormality	No.	%
Diffuse dysrhythmia	14	64
Bilaterally synchronous disturbances	8	36
3/sec. wave and spike ..	0	0
3/sec. variants	1	5
6/sec. rhythms and variants	7	31
Focal abnormality	0	0
Total ..	22	100

8. *T.D.E. Dizzy Spells with Diffuse Dysrhythmia and Convulsion under Hydration.*—This airman, aged 18, complained of spells which occurred very frequently—about six to seven times a week for the past year. The spells were described as " dizziness " or " moments of blankness." He could usually feel the spell coming on and it lasted from one to a few minutes ; after it he felt slightly depressed.

Hydration was carried out to see if these attacks could be witnessed, and E.E.G. examination was done before and after. During the hydration test, a seizure was observed by the nurse as follows : The patient appeared confused for a few moments and this was followed by a generalized tonic convulsion, then a mild clonic phase. After this, he went into a deep sleep from which he could not be roused for about half an hour.

The resting E.E.G. (Fig. 8) showed a poorly organized background consisting largely of irregular slow waves. With hyperventilation there was a rapid increase in slow-wave discharges with a tendency for them to become rhythmic and paroxysmal. During hydration, the E.E.G. showed diffuse irregular slow waves and with hyperventilation, there were high voltage 3 to 6 per second waves which frequently became rhythmic and persisted longer than half a minute after overbreathing stopped.

Comment.—It is apparent that this example is a link between patients who have mild transient episodes without loss of consciousness and those who under certain circumstances (hydration in this instance) may have a generalized convulsion with loss of consciousness. Both groups have a similar type of diffuse E.E.G. dysrhythmia and the convulsion is a more severe clinical manifestation of the same disorder which causes the sudden transient dizziness or " moments of blankness."

Discussion

The association between interseizure E.E.G. abnormalities and syncopal spells confirms what has long been suspected, namely, that in some patients syncope may be primarily cerebral in origin and epileptic in character.

In syncope from any other cause, loss of consciousness is secondary to cerebral ischemia resulting from a sudden decrease in intracranial blood supply (Weiss, 1935 ; Rossen, 1947 ; Engel, 1945). This change is accompanied by the sudden appearance of E.E.G. abnormalities which disappear with the return of consciousness. However, the patients described in this report had a pathological E.E.G. between spells, the abnormalities were of the same kind as occur in clinical epilepsy, and responded in the same way by increasing during hyperventilation and hydration.

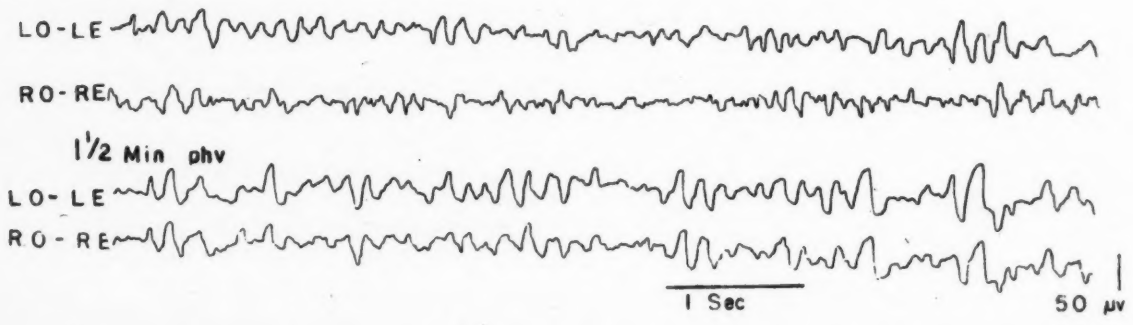


FIG. 7.—Patient A.G. Spells of giddiness, sweating, and " blackout " with 6 per second waves. The markings are similar to previous records. The lower two lines show the persistence of exaggerated amount of abnormality one and a half minutes after the end of hyperventilation.

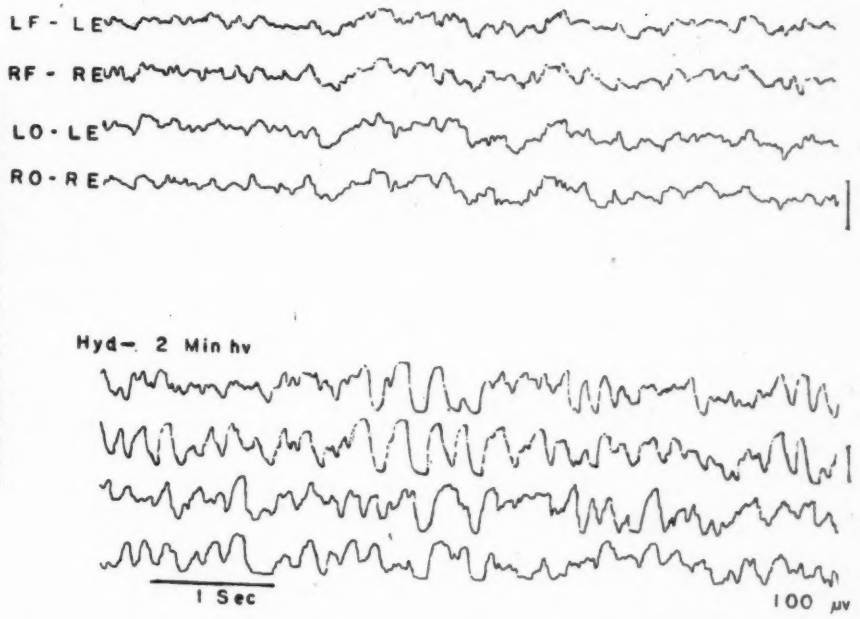


FIG. 8.—Patient T.D.E. Spells of dizziness and moments of blankness with diffuse dysrhythmia and convulsion under hydration. LF and LO are left frontal and occipital records to the left ear. RF and RO are right homologous records. Under hydration and 2 minutes of hyperventilation as shown in the lower four lines the slow waves become much higher in voltage and organized into rhythmic bisynchronous patterns.

The occurrence of a pathological E.E.G. in the resting state is of decisive value in differentiating between simple syncope and epileptic states (Schwab, 1943 ; Silverman, 1944 ; Roseman, 1944) and in patients suspected of epilepsy, even minute and evanescent E.E.G. disturbances (Williams, 1944) may indicate epileptic activity.

Clinically, the patterns of the spells are exactly like the vagal and vasovagal attacks described by Gowers (1907), including the fact that they often occur with physical and emotional strain and are frequently seen in patients with neuroses. Of particular historical interest, is the fact that in a footnote Gowers stated that " some of the symptoms have been described in other associations by Freud . . . and others, especially in connexion with ' neurasthenia ' ! "

Wilson (1928, 1940) has suggested that such spells are due to discharges from the neurosympathetic ganglia around the third and fourth ventricles and proposed the term " periventricular epilepsy." The character of the E.E.G. abnormalities seen in many of these patients lends considerable support to this hypothesis. Most commonly (in 65 per cent.) the alpha rhythm was absent and replaced by diffuse slow waves or mixed fast and slow activity. Experimentally, bilateral disappearance of the cortical alpha occurs following hypothalamic lesions (Kennard, 1943 ; Obrador, 1943) and it is replaced by generalized irregular slow waves. Electrical stimulation of the hypothalamus (Grinker and Serota, 1938 ; Murphy and Gellhorn, 1945 a and b) produces a marked generalized excitatory effect over the entire cortex bilaterally with facilitation to simultaneous subclinical cortical stimulation. Localization of the functional disorder to the hypothalamus in these patients would explain both the E.E.G. findings and the clinical manifestations.

The second largest group of patients (22 per cent.) had bisynchronous 6 per second waves and variants, and it has recently been shown both clinically (Cobb, 1944 ; Walter and Dovey, 1944 ; Lennox and Brody, 1946) and experimentally (Jasper and Drooglever-Fortuyn (1947) that this type of abnormality is also subcortical in origin.

In a small number (6 per cent.), the abnormal discharges were localized to the temporal region and episodes of bizarre behaviour occurred which were probably ictal automatisms, in addition to spells with loss of consciousness. It is of interest that from the nature of these spells, they would be called " psychomotor seizures " according to the classification of Gibbs and others (1938), yet 4 to 7 per second waves were not the most prominent feature of the interseizure record. The abnormality was mainly random 1 to 3 per second slow waves with some sharp discharges.

It is felt that the twenty-two patients without loss of consciousness had a milder type of the same disorder as was present in the ninety-two who had a history of loss of consciousness. A more severe manifestation is the appearance of generalized convulsions which occurred in one instance

(example 8, T.D.E.) during hydration. A group of patients with similar E.E.G. abnormalities in whom infrequent convulsions occurred spontaneously are reported elsewhere (Kershman and Elvidge, 1948).

The question of a name for this syndrome requires consideration. A year ago similar patients were reported (Goodwin, 1947; Proctor, 1947) who showed vasomotor instability, changes in consciousness, and variations in the E.E.G. They were included with a group of patients who had other and quite different clinical manifestations, such as headache, personality disorders, grand mal, and a condition called "hysteroid Jacksonian" attacks. Because the E.E.G. between spells showed what was described as "psychomotor activity" and "alpha variants," the term "epileptiform syndrome" was applied to all these conditions.

The term "psychomotor activity" is derived from Gibbs and others (1937) who discovered that clinical "psychomotor attacks" were accompanied by slowing of the electrical activity of the brain (usually illustrated by high voltage 4 to 7 per second waves). This E.E.G. pattern was called "psychomotor discharge" and the name became attached to 4 to 7 per second waves wherever and whenever they occurred. The increasing use of electro-encephalography in a wide variety of different neurological and psychiatric conditions has demonstrated similar abnormalities in many of them. As a result, many clinical states, including headache, behaviour problems in children, emotional instability, psychopathic personality, etc., showing so-called "psychomotor discharge" have been referred to as "epileptoid," "epileptiform," or "epileptic equivalents." By gradual extension these conditions have been allied to what Gowers described as "the borderland of epilepsy."

It is felt that the term "psychomotor activity" as applied to the E.E.G. is quite misleading in its implications. Frequencies at 4 to 7 per second commonly occur in a wide variety of conditions without any suggestion of clinical epilepsy (Jasper, Kershman, and Elvidge, 1940; Cobb, 1944; Walter and Dovey, 1944; Finley and Dynes, 1942). The commonest form of abnormality in any kind of intracranial neoplasm, for example, was 4 to 7 per second activity (Kershman, Conde, and Gibson, in the press) and bore no relation to the occurrence of "psychomotor" or any other type of epilepsy. So-called "psychomotor epilepsy" or automatisms may be either ictal or post-ictal and related to lesions involving either the temporal or frontal regions (Penfield and Erickson, 1941; Penfield, in the press). In many instances, as illustrated by example 5, G.A.C. above, patients with spells that might be called "psychomotor" do not have 4 to 7 per second waves between attacks and may only show slower activity, sharp waves, or spikes localized to the temporal regions (Jasper and Kershman, 1941).

In clinical epilepsy, the chief value of the E.E.G. is to localize, if possible, the source of the "abnormal excessive neuronal discharge," and if properly used it does so in very many instances. What the relation is between the electrical activity and the occurrence of a clinical seizure is not known. Until this is clearer, as well as for other reasons, it would seem inadvisable to extend the clinical meaning of the term "epilepsy" to embrace a number of different conditions in which there may be E.E.G. abnormality; especially if the clinical manifestations do not have the periodic and explosive quality of a seizure and the form of the E.E.G. abnormality is not exclusive to epileptic states. In the case of "alpha variants" it is not even certain that an E.E.G. abnormality is present.

There still remains the problem of terminology for the syndrome consisting of syncopal spells with an abnormal E.E.G. and epileptic origin. Though the ætiology is not known, it is probably related to cryptogenic or idiopathic epilepsy.

In most of these patients, however, the syncopal spells were infrequent and no convulsions had occurred. The term "epilepsy" carries with it important personal, social, and economic stigmata, which, though frequently unjustified, must be faced realistically by the physician who attaches this label to a patient. For these reasons the term "cerebral syncopal seizures" or "encephalosyncope" is suggested. This designation is descriptive of the origin and clinical nature of the seizure. It is felt that the condition has its localization in or near the hypothalamus and is related to other forms of idiopathic epilepsy. If the attacks become frequent and convulsive, as it may in some instances, then the term idiopathic epilepsy becomes inevitable.

Summary and Conclusions

1. One hundred and fourteen patients have been described having syncopal spells and episodes of transient dizziness, blurring of vision, "blackout," abdominal sensations, and weakness with or without loss of consciousness. No definite convulsions occurred in any of them although in one instance a seizure was produced during the hydration and pitressin test.

2. All these patients had pathological E.E.G. records between spells, the commonest type of abnormality being a diffuse dysrhythmia (65 per cent.).

3. These spells were essentially the same as the vagal and vasovagal attacks described by Gowers,

and the E.E.G. disturbances indicate that they are fundamentally epileptic in character.

4. The form of the pathological E.E.G. abnormality and the character of the spells suggest a subcortical and probably hypothalamic origin.

5. For this reason, and the fact that convulsive seizures do not occur, and also because of the personal and social stigmata attached to the diagnosis of epilepsy, the term " encephalosyncope " is suggested as a diagnosis for these patients. It is in effect a mild form of idiopathic epilepsy.

6. In several instances a focal abnormality in the temporal region can be isolated by the E.E.G. and these patients have ictal automatisms. These are cases of focal cortical temporal lobe seizures.

7. The term " psychomotor discharges " is misleading when used to describe an E.E.G. abnormality since so-called " psychomotor " attacks are not always associated with such discharges and vice versa. Attempts to correlate this pattern of E.E.G. abnormality with clinical syndromes may lead to considerable confusion.

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THE INTELLIGENCE OF PATIENTS WITH FRIEDREICH'S ATAXIA

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Most references to the intellectual status of patients with Friedreich's ataxia comprise vague clinical impressions. General statements about this aspect of the patients were, however, made early in the history of the disease. Friedreich himself (1863) noted the absence of intellectual defect in his cases. This view held sway for a long time. Raymond (1898) emphasized " pas de troubles intellectuels " as a characteristic of this disorder, and Whyte (1898) went so far as to say, " Mental defect seems a much more important sign than the retention of the knee-jerk in making one doubt a diagnosis of Friedreich's ataxia." In much the same strain Ladame (1890) wrote, " Some authors think they (i.e., patients with Friedreich's ataxia) always suffer from an arrest of intelligence. The case which we relate proves the contrary."

Turning to individual case histories we find that cases with " average " or " good " intelligence have been described by many authors (Gowers, 1881 ; Taylor, 1894 ; Mackenzie, 1894 ; Clarke, 1889 ; Small, 1895 ; Speer, 1921).

Cases with notably superior intelligence have been described by several authors. Thus Tressider's (1893) case was head boy of a public school, and took an honours degree at Cambridge. Bramwell (1897) described his patient as being " very intelligent," and Moody (1910) described one of his patients as " very intelligent."

Low intelligence in patients affected with Friedreich's ataxia has been noted by Power (1882), Ogilvie (1908), Speer (1921), Walter and Roese (1926), Schröder (1937). The " three cases of genetous idiocy associated with Friedreich's ataxia," described by Nolan (1895) and often quoted in this connexion, would appear, in the light of further investigations by Batten and Wilkinson (1913–14), to have been cases of Pelizæus-Merzbacher disease.

Hanhart (1923) said that one encounters in these cases of Friedreich's ataxia a deterioration of intellect and affect. He saw no cases of idiocy, and severe grades of mental deficiency only where the disease had been of very early onset. He warned against easy guesses at the intelligence level of these patients. He said that, just as many imbeciles are over-estimated intellectually by some deceptive verbal facility, so may the hereditary ataxias be underestimated by their reticence.

Bell and Carmichael (1939) wrote on this subject :

> " There is no doubt that patients . . . may retain their mental faculties unimpaired, and may occasionally show a mental alertness above the average ; but a very considerable proportion of cases . . . do show signs of mental deterioration . . . when such defect occurs it is not a late symptom of the disease but is often conspicuous from the early stages of the affection and is not, in marked cases, demonstrably contributed to by the cultural limitations imposed on the patient by reason of the ataxic disease itself . . . A few cases, some half dozen perhaps, undoubtedly showed signs of rather severe mental deterioration, which was probably associated with their ataxia disease and might presumably be attributed to an extension of its pathological processes ; . . . I considered the possibility of measuring the intelligence quotient on this series of patients but decided that tests made under a state of nervous tension owing to the circumstances of our visit, and tests which were likely to be influenced by the cultural restrictions necessitated by the disease, could contribute no positive information concerning the question of mental deterioration in cases of hereditary ataxia, and might even be misleading."

The first attempt to apply standard tests to such cases seems to have been that of Landsbergen (1912) in three cases of familial cerebellar ataxia. These tests were for memory, conceptual ability, and comprehension. There was no scoring given, tests and answers being quoted verbatim. The patients were of very low intelligence. Since then only two other investigations along quantitative lines seem to have been made, that by Sjögren (1943) and that by Blöchlinger (1946). The latter may be discussed first.

Blöchlinger was concerned to find, by tests of mental function, further evidence in support of Bleuler and Walder's (1946) view of the nature of mental change consequent upon diffuse brain damage at an early age. His material consisted of six chronic cases of Friedreich's ataxia which had been admitted to a general hospital purely on account of their physical disability. It is of interest to note

that one of these patients showed a frankly psychotic picture, with irritability, mood changes, and delusions of influence and persecution. Although these patients were given batteries of test questions, the answers to which are reported verbatim, no attempt is made to score these answers. Just as no measure of intellectual level which could be used for comparative purposes emerges, so there is no attempt to distinguish between present ability and a level of native intelligence from which the patient may have deteriorated during the course of his illness. Blöchlinger's conclusions concern chiefly conceptual ability, memory, and attention (said to be unchanged) and a slowing of thought, poverty of ideas, and tendency to perseveration. Critical ability, judgment, and native intelligence are said to be deteriorated.

Sjögren (1943) studied a long series of 188 cases of heredo-cerebellar ataxia, eighty-four of these being cases of Friedreich's ataxia. These were examined chiefly from the neurological and genetic standpoints, but some tests of mental function were given to these patients. The extent of the testing is not too clear from Sjögren's account. One series of nine questions was put, of the type used in the comprehension section of the Wechsler scale. In addition some tests of serial subtraction were given, and as, in some cases only, he gives a mental age for the patient, one presumes that some other tests (not specified in the text) may have been given. There is no evident scoring, however, except for those cases where a figure is given for mental age. From his series Sjögren concluded that in Friedreich's ataxia: (1) 15 per cent. of cases showed oligophrenia; (2) 58 per cent. showed progressive dementia.

Most recently Knoepfel and Macken (1947) claim that ten out of fifteen cases showed feeblemindedness, though they give no details whatsoever in all but two of these patients.

Clearly there has been much conflict of opinion in a region where clinical observation may be helpfully supported by more objective measurement.

Material and Methods

An investigation into the mental state of twenty cases of Friedreich's ataxia was carried out. Personality changes and frank psychoses occurred among these patients, and will form the subject of a later publication. In this present paper consideration is given to the intellectual status of these patients as gauged from their performance on various psychological tests, and from clinical estimates based on their behaviour and personal history (in particular their scholastic and work records).

Three of these patients were originally seen in the Maudsley Hospital, to which they had been admitted because of their mental state. The remaining seventeen were either patients in London County Council hospitals for chronic sick (seven cases), confined to their homes (four cases), or at work (six cases). No selection was exercised in the choice of these patients; all who could be traced were investigated and recorded. In every case the diagnosis had originally been made by a neurologist of some distinction, and frequently the patient had been seen at various times by more than one such consultant. Each case was examined physically and mentally, relatives were interviewed, and in some cases a social worker visited employers to gather additional information.

Three psychological tests were used as a routine, though for various reasons it was not possible to apply all three to all the patients. The Mill Hill vocabulary test, Raven's progressive matrices, and the verbal half of the Wechsler Bellevue scale were the tests used. The Mill Hill vocabulary test (Raven and Walshaw, 1944) offers to the subject six alternative choice synonyms for each of the thirty-four test words. The test was originally standardized on school children and military personnel, and the results may be expressed in I.Q. Raven's progressive matrices test is very well known by reason of its adoption by the War Office for the testing of men in the General Service Corps in the 1939–45 war. It is a non-verbal test, highly saturated with "g"—the factor of general intelligence—and in consequence it tests present fluid ability with little reference to previous experience. The Wechsler-Bellevue scale comprises, in its verbal half, five sections (comprehension, arithmetic, digit repetition, similarities, and vocabulary), so that it tests intelligence from many angles.

These tests were regarded as complementary to clinical examination of the patient. By taking into account all the clinical data, including information as to school and employment record in each case, a clinical estimate was formed of intellectual status and the presence or absence of dementia. The matrix I.Q. expressed as a percentage of the Mill Hill I.Q. gave a conceptual quotient (C.Q.). C.Q.'s were obtained on eighteen patients who did both the Mill Hill and matrix tests. The Mill Hill test was unfortunately omitted in Case 2 (who subsequently died), whilst Case 17 was unable to read and, therefore, was unable to do the test at all. The Wechsler-Bellevue scale was applied in eighteen cases, being omitted for various incidental reasons in two cases.

The Mill Hill and matrix tests were also given to a miscellaneous group of fifteen chronic invalids, who had been in hospital for many years. Such invalids were afflicted with chronic rheumatism, heart disease etc., only those with diseases of the central nervous system being omitted. These patients were found in the wards of the hospital where were our Cases 7, 8, 9, and 10. The average age of the control group was higher than that of the Friedreich's ataxia group, and the average duration of invalidism was longer. Since the matrix test results were corrected for age the former factor was taken into account, and the longer duration of invalidism was a difference in the right direction, since the aim of using such a control group was to find how far any significant results of our testing could be explained simply as the result of invalidism, or could be related to

the particular disease (Friedreich's ataxia) affecting the group in which we are interested.

Patients in hospitals were visited there and tested; patients who were able to do so came up to the out-patients department for examination, those confined to their homes were visited for this purpose.

The choice of these particular tests was determined by several factors. Time was important, since many of these patients were visited in their homes and visits could not be prolonged to the point of interfering with domestic routine. Physical incapacity of the patients was another important factor. On this account Koh's blocks could not be used as a test, since some of the patients lacked the necessary power to lift and arrange the material. On the whole the tests selected worked well in these respects, and all the patients except one were able to use a pencil well enough to write a number or underline a word.

One final point need be mentioned here. All tests were untimed, so that the slowness in speech and response so well known in these cases was not in itself a factor influencing a test-score adversely.

Results

The results of intelligence testing are given in Tables I, II, and III. No patient showed idiocy or imbecility, nor did any patient show a sufficient degree of mental defect in the statutory sense to justify the use of that term in describing them.

Reference to Table I shows that only two cases (Nos. 6 and 17) had an I.Q. of less than 75 on the Mill Hill test. One of these (Case 17) was unable to read and, therefore, had no score on the test, but even including him the figure is not significantly different from the approximate 5 per cent. of the general population who would fall below I.Q. 75 on this test. On the Wechsler Test (a slightly different group) no patient had an I.Q. level of less than 75. From these observations it is possible to conclude that there is no evidence that mental deficiency is commoner among cases of Friedreich's ataxia than among the general population.

This point may be put to the test in another way, though the smallness of our group is not very conducive to the provision of strong proof. The mean I.Q. of the series, on the Mill Hill test, is 101·2, with a standard deviation of 13·79 and a standard error of 4·12. This is not significantly different from the population mean of 100. Here again there is no evidence to support the view that the initial or native intelligence of people who develop Friedreich's ataxia is significantly different from that of the general population.

In considering the more difficult question of the occurrence of dementia, reference must first be made to our clinical reports. Dementia presents itself to clinical observation in loss of recent memory, intellectual weakness (the inability to make the fine comparisons and discriminations of the healthy mind), and disturbances of mood, such as euphoria. Later the loss of acquired good habits in relation to feeding and dressing may be obvious. In no case was any gross dementia clinically appreciable, but minor indications of such a process were evident in some of the patients examined. Thus Case 8 showed some impairment of recent memory as compared with old, and loss of attention and concentration in the serial 7 test. Some euphoria was observed. Conceptual quotient was 83. Case 10 showed some impairment of attention and concentration on the serial 7 test, and marked euphoria. Conceptual quotient in her case was 84. Case 12 showed poor ability to recall a name and address after five minutes, and poor general knowledge in face of a relatively high score on the Mill Hill test (I.Q. of 92). The conceptual quotient here was 76.

In certain other cases (182) it was suspected that dementia was present, but it was not possible to make this diagnosis clinically for various reasons (thus Case 18 was almost completely paralysed, whilst Case 2 had long periods of confusion while in hospital).

TABLE I

FRIEDREICH'S ATAXIA: 20 CASES

Case no.	Sex	Age (years)	Age at onset (years)	Duration (years)	Mill Hill I.Q.	Matrix I.Q.	C.Q.	Wechsler I.Q.
1	M	15	13	2	97	90	93	104
2	F	21	19	2	—	66	—	75
3	F	23	11	12	100	83	83	—
4	F	24	14	10	114	95	83	96
5	M	27	14	13	119	98	82	—
6	M	35	21	14	71	73	103	78
7	F	39	13	26	122	118	97	115
8	F	38	20	18	89	74	83	81
9	F	43	21	22	97	95	100	101
10	F	35	19	16	115	97	84	111
11	M	25	11	14	100	94	94	108
12	M	45	14	31	92	70	76	95
13	F	27	13	14	92	88	96	94
14	F	32	13	19	122	117	96	117
15	M	28	17	11	108	104	96	114
16	M	28	13	15	108	95	88	111
17	M	18	10	8	—	71	—	82
18	M	29	10	19	86	69	80	79
19	M	23	10	13	97	88	91	101
20	F	26	12	14	92	80	87	98

Sufficient has been said here, however, to enable us to draw the conclusion from clinical examination that some dementia—of no great degree for the most part—occurred in some three or four of our series, and was suspected in others.

If now we turn to Table I, it will be observed that the C.Q. is below 100 in all but two cases. Considering only those eighteen cases who did both Mill Hill and matrix tests the mean C.Q. is 90, the standard deviation is 8·1, and the standard error 1·9. The first point of interest here is the low standard deviation, which stamps the Friedreich ataxia patients as a remarkably homogeneous group in this respect. Secondly, the mean of 90 is significantly different from that of the general population (100), since Critical ratio $= \frac{100 - 90}{1{\cdot}9} = 5{\cdot}3$, a high degree of significance.

Similar comparison of the control group of general invalids (Table III) shows that the mean is within one of 100 so that there is no significant difference.

It would, therefore, seem that the deficit shown by the Friedreich group is not to be accounted for on the score of general invalidism. Clearly the low C.Q. in the cases of Friedreich's ataxia is due not to high Mill Hill scores, but to low scores on the matrix test. The I.Q.'s derived on these two tests may be compared, since these two particular tests have the same standard deviation. The relevant figures for these I.Q.'s in all the Friedreich ataxia cases who did both tests is given here:

	Mill Hill	*Matrix*
Mean	101·2	90·4
S.D.	13·79	12·34
S.E.	4·12	3·00

Critical Ratio = 3·3 p = ·002

This is additional support for the conclusion that the deficit as manifested in low C.Q. is not due to chance factors. Similar treatment of the Mill Hill and matrix I.Q.'s of the control group of general invalids shows no significant difference. There is no significant correlation between the extent of this deficit and the duration of illness or age of the patient. This would argue against the progressive nature of deterioration in these cases, and would accord with the clinical impression of Bell and Carmichael (already quoted) that where dementia occurs it tends to appear early in the disease

The deficit so revealed might be explained on the basis of a specific defect. Cases of Friedreich's ataxia show, in addition to ataxia of the limbs, a frequent nystagmus. A specific disability for handling material in the form of geometrical patterns (as involved in the matrix test) cannot be ruled out of court in the absence of further evidence

TABLE II

FRIEDREICH'S ATAXIA: 17 CASES
WECHSLER-BELLEVUE SCALE: WEIGHTED SUB-TEST SCORES

Case no.	Comprehension	Arithmetic	Digits	Similarities	Vocabulary	Total
1	12	6	7	11	13	49
4	8	9	6	9	12	44
6	6	6	3	5	6	26
7	12	12	9	12	14	59
8	10	3	4	4	8	29
9	9	9	9	8	10	45
10	14	10	6	14	11	55
11	14	9	6	14	11	54
12	8	9	7	7	8	39
13	7	10	6	11	8	42
14	13	13	7	14	14	61
15	11	17	9	12	11	59
16	14	10	6	14	12	56
17	8	9	6	5	5	33
18	8	6	4	5	6	29
19	11	9	10	9	9	48
20	9	6	11	8	11	45

TABLE III

CONTROL GROUP OF 15 CHRONIC INVALIDS

Case	Age (years)	Duration (years)	Mill Hill I.Q.	Matrix I.Q.	C.Q.
D.W.	51	9	94	140	150
J.D.	40	12	115	101	88
G.F.	24	11	94	106	113
P.L.	20	7	97	110	114
E.G.	34	8	106	102	97
P.R.	24	24	92	95	103
E.A. ..	47	36	84	67	80
E.C.	57	12	100	114	114
M.B.	45	34	124	75	60
R.W. ..	47	12	97	106	109
C.A.	50	14	103	112	109
M.H.	51	1	81	92	114
N.P.	44	9	103	70	68
L.S.	39	10	74	75	101
F.A.	38	14	84	71	88
Means ..		14	96·3	95·7	100·5
S.D. ..		9·4	13·3	17·6	21·9

to the contrary. Material derived from our Wechsler Bellevue tests (Table II), however, renders this view untenable. Here the five sub-test weighted scores have been given in detail for the seventeen patients who did this test. The means of the scores on digit repetition on the one hand, and vocabulary on the other, have been compared, and a critical ratio of 4·96 has been obtained. This is very highly significant.

It is generally accepted (Wechsler, 1944) that in testing patients who are demented this type of score, that is, a low digit repetition as compared with vocabulary score, is obtained. The difference is clearly not due to a high vocabulary score (see Mill Hill test results), so that we are justified in concluding a significantly low digit repetition score.

Weighing all the evidence of our psychological testing, we may conclude that a significant deficit is shown by the group of patients with Friedreich's ataxia, and such deficit is not to be accounted for merely by invalidism and the deprivation or lack of social opportunity which invalidism carries in its train.

Combining these test results with our clinical observations, which suggested dementia in a certain number of cases, we may justifiably equate such deficit with the occurrence of dementia.

We would, therefore, amend Sjögren's conclusions, which were by no means satisfactory in their derivation, by declaring that in our series of cases of Friedreich's ataxia there is no evidence to suggest that those who are marked down for the disease are intellectually different from the general population, but that patients affected with this disease show, as a group, significant dementia of no great degree.

Summary

The intelligence of twenty patients suffering from Friedreich's ataxia was measured by means of the matrix, Mill Hill, and Wechsler-Bellevue tests. A clinical estimate of intellectual deterioration was made in each case.

Similar testing was also carried out on a control group of seventeen chronic invalids from other causes.

No evidence was found to suggest that those marked down for Friedreich's ataxia are intellectually different from the general population, but patients affected with this disease show, as a group, significant dementia of no great degree.

This dementia appears early and is not progressive.

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DEVELOPMENTAL DEFECTS OF THE CISTERNA MAGNA AND DURA MATER

BY

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Introduction

Cerebral defects of developmental origin, apart from those involving the nervous parenchyma, are to be found chiefly in the neighbourhood of the roof of the third ventricle. The complex developmental evolution of the structures in this region may predispose to imperfect development, whether the cause be some variety of damage which impairs development, or some genetically transmitted factor.

The suprapineal recess varies considerably in size, and in ten of five hundred cases it was found to be much larger than usual. The two leaves which fuse to form the septum pellucidum sometimes remain separated and a fluid-filled cavity separates the lateral ventricles. Sometimes one or both walls of this cavity are fenestrated, thus allowing communication between the lateral ventricle and the cavum septi pellucidi. The arachnoid-lined space in the velum interpositum is obliterated during normal development, but sometimes persists into adult life. Finally, the corpus callosum and fornix may be absent or may cease to develop at an early stage.

The cisterna magna also is subject to considerable variation in size and shape, due to causes active during development. The shape and extent of the cisterna magna are important in the performance of encephalography, and the recognition of abnormality is important if ventricular filling is to be secured in the patient in whom an unusual state exists. The lack of recognition of the anomalies to be described is due to the difficulty of delineating the cistern in specimens, for without floating the arachnoid away from the brain it is difficult to delimit the periphery of the cistern. It is only when gas in the cistern clearly delimits it that these variations can be recognized.

Normal Anatomy of the Cisterna Magna

As the arachnoid membrane passes upwards from the spinal canal through the foramen magnum to enclose the contents of the posterior cranial fossa it becomes more extensive. Anteriorly the subarachnoid space suffers no interruption in front of the medulla and pons. Thus, during encephalography, gas is able to pass upwards to reach the interpeduncular cisterns and thence the cerebral subarachnoid space (Fig. 1). Posteriorly and laterally, however, the arachnoid membrane is closely applied to the pia mater on the inferior surface of the cerebellum. Thus, in this direction, the upward passage of gas is blocked (Figs. 1 and 13a). The attachment over the vermis in the median plane posteriorly is usually at a higher level than the attachment to the laterally placed hemispheres. In front, the close apposition of pia and arachnoid ceases at the ventral border of the cerebellum, a wide subarachnoid space which is continuous with that over the anterior surfaces of the medulla and pons being found in the cerebellopontine angles.

The term cisterna magna* is applied to the portion of the wide subarachnoid space below the inferior surface of the cerebellum, behind the medulla, and above the dura and arachnoid over the lower and medial part of the occipital bone. The foramen of Magendie lies at the apex of the anterior part of the cistern, at a higher level than the lower surface of the vermis. The normal disposition in this region is responsible for the filling of the ventricles when gas is introduced with the head in a flexed

* In the original description, the cisterna magna cerebellomedullaris includes that part of the subarachnoid space anterior and lateral to the medulla. However, it facilitates description, and is common usage, to apply the term cisterna magna only to that part behind the medulla. The anterior part may well be called the medullary cistern.

position. The gas rises behind the cervical spinal cord and then through the dorsal part of the foramen magnum to the cisterna magna. It passes to the upper part of the cistern, and when the gas-fluid level sinks below the lowest part of the vermis gas will flow forwards and upwards, between the cerebellar tonsils, to the foramen of Magendie and thus into the fourth ventricle. Gas in this position is seen clearly in lateral views (Fig. 1). In axial views (films taken with the central ray directed, with varying inclination, along the median plane of the skull) it is seen as a dense, narrow shadow in the mid-line, widening below into the shadow of the remainder of the cisterna magna and above into that of the fourth ventricle. Some gas rises directly to the anterior part of the cistern, anterior to the sill provided by the vermis, and thus to the foramen of Magendie, the amount so doing increasing as the head becomes more erect.

Variations in the Cisterna Magna : Recognition during Encephalography

The extent of the cistern over the inferior surface of the cerebellum varies considerably. In the majority of cases the cistern extends about 2·5 cm. above the foramen magnum along the inner table of the occipital bone, reaching a point midway between the posterior lip of the foramen magnum and the internal occipital protuberance (Fig. 1). The depth (that is, the axial extent) is usually 5 mm. The cistern is sometimes small, sometimes considerably larger. Only when the cistern is large is it well seen in axial views. Owing to its position over the lower part of the occipital table, the lateral extent of the shadow is best seen in occipito-vertical views taken with the head well flexed before gas has entered the ventricles or anterior subarachnoid spaces. The width is very variable. Sometimes the shadow is about 2 cm. wide; sometimes much broader. The dense median shadow of the inferior occipital crest often divides the shadow into two more or less symmetrical halves (Fig. 2).

The cistern was found to extend as high as the internal occipital protuberance four times in one hundred cases (Fig. 3). In these cases the depth and the width of the cistern were usually larger than normal. Such a cistern causes a dense shadow during encephalography, owing to the large volume of gas which it contains. This may lead to confusion in interpretation of encephalograms unless the significance of the shadow is recognized. Such a large cistern may, by its capacity, interfere with the early filling of the ventricles. Thus 10 or 12 c.cm. of gas may be introduced before any passes into the ventricles. Gas begins to enter the fourth ventricle when the dorsal part of the cistern is full, but ventricular filling may be secured at an earlier stage by dorsiflexing the head. The cistern is thus brought to a lower level than the foramen of Magendie, and gas is decanted into the fourth ventricle.

In some cases the lateral limits of the cistern are unduly wide and are placed at a higher level than the foramen of Magendie. Gas entering dorsally will not be directed to the foramen of Magendie, but will flow forwards at a higher level to the cerebello-pontine angles and thus into the pontine cisterns. This is a commonest cause of failure to fill the ventricles during encephalography. Unless a special manœuvre is employed, gas will not then enter the ventricles during encephalography. The head is fully flexed during periods of introduction of gas and slowly dorsiflexed between such injections. In such full flexion the foramen of Magendie is higher than the point on each side at which the cisterna magna decants into the lateral recesses of the medullary and pontine cisterns.

Secondly, the pia and arachnoid may not fuse over the inferior surface of the cerebellum, hence the usual barrier at the upper level of the cisterna magna does not exist (Figs. 4 and 13c). Gas entering dorsally passes cranially around the cerebellum to the cisterna venæ magnæ cerebri and thus to the cerebral subarachnoid space. In normal cases the subarachnoid space over the superior surface of the cerebellum may fill with gas from the cisterna venæ magnæ, but no gas passes from there down to the inferior surface of the cerebellum at a lower level (Fig. 5). When the cisterna magna is not closed above, gas reaches the superior surface of the cerebellum without passing along the ventral and ambient cisterns (Fig. 4). In this case, the gas is not directed to the foramen of Magendie, hence ventricular filling is difficult to secure. If the head be kept erect, instead of flexed, some gas rises directly to the foramen of Magendie and enters the ventricles.

The anomaly which is the subject of this paper was first seen four years ago. The cisterna magna was found to extend above the inion, almost to the apex of the occipital bone (Fig. 6a). Thus, its apex was considerably above the usual level of the tentorium. In addition to extending unusually high, the cistern was also very wide in its lower part (Fig. 6b). Fifteen c.cm. of gas were introduced without the appearance of ventricular shadows. By dorsiflexing the head the gas could be decanted through the foramen of Magendie into the ventricular system. Some three years later a second instance was found during encephalography (Fig. 7), and a year later a third exactly similar appearance (Fig. 8) was found. In the last instance it was possible to

FIG. 1.—Normal cisterna magna in lateral view. The uninterrupted upward passage of gas anterior to the spinal cord, medulla, and pons is shown in contrast to the limitation behind by the close apposition of arachnoid and pia over the cerebellum. Gas may escape from the cisterna magna by passage (*a*) forwards and upwards to the fourth ventricle through the anterior part of the cisterna magna (seen as a dense column leading up to the fourth ventricle), or (*b*) forwards at a lower level into the medullary cistern.

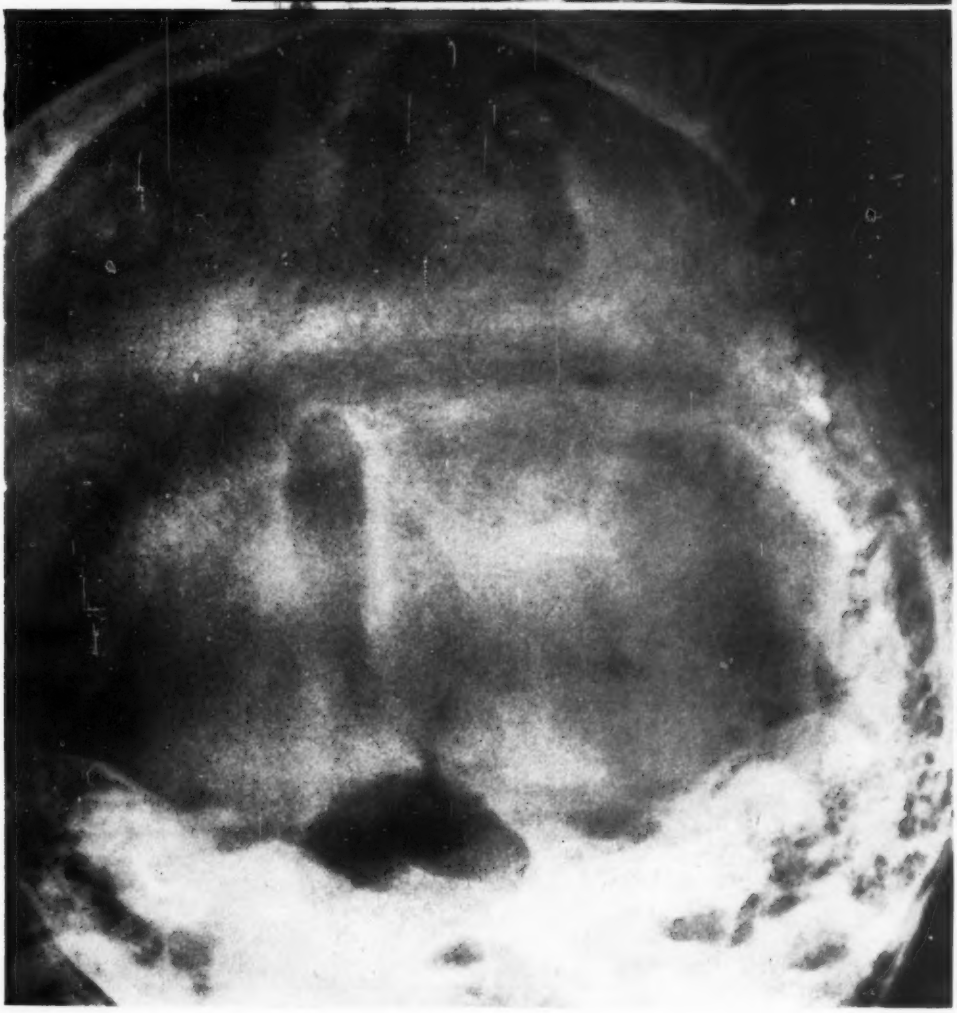

FIG. 2.—Large cisterna magna in an occipito - vertical film at an early stage of encephalography. The median shadow of the anterior part of the cistern is seen.

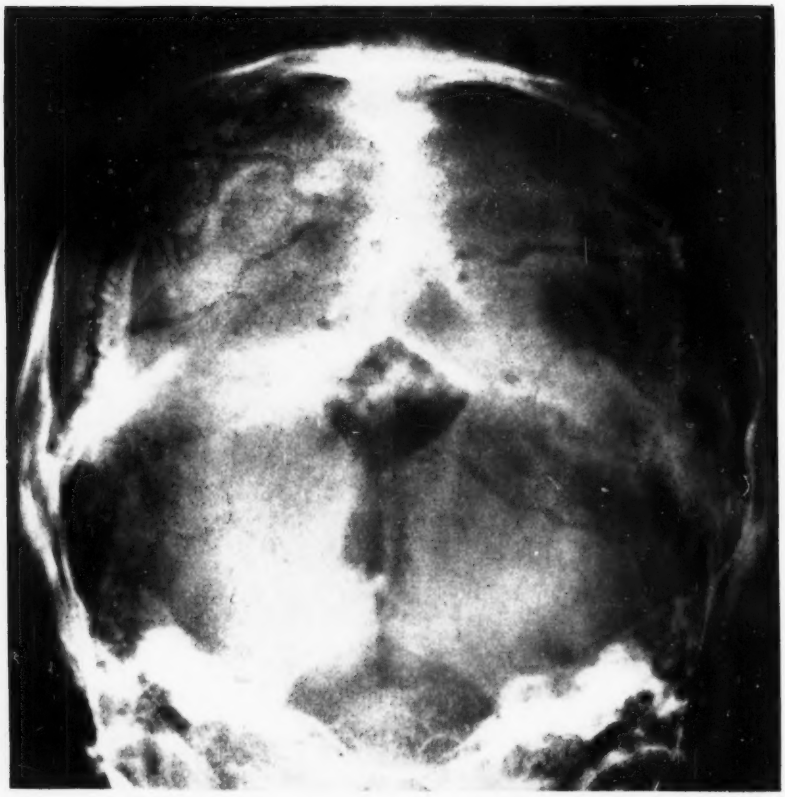

FIG. 3.—Large cisterna magna reaching the inion.

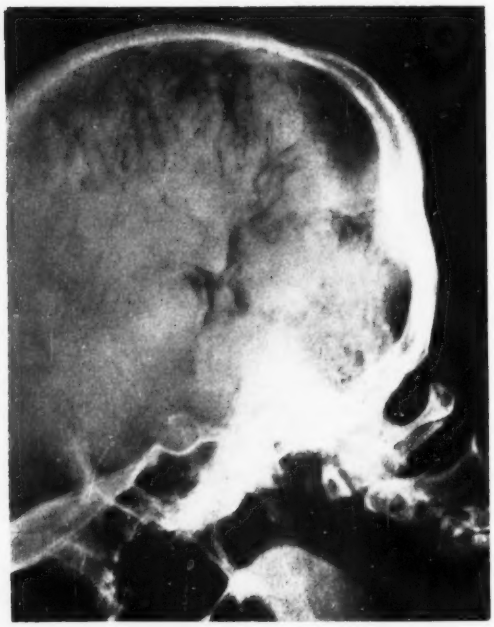

FIG. 4.—Defective occlusion of the upper limit of the cisterna magna, allowing gas to pass freely over the cerebellum to the cisterna venæ magnæ cerebri.

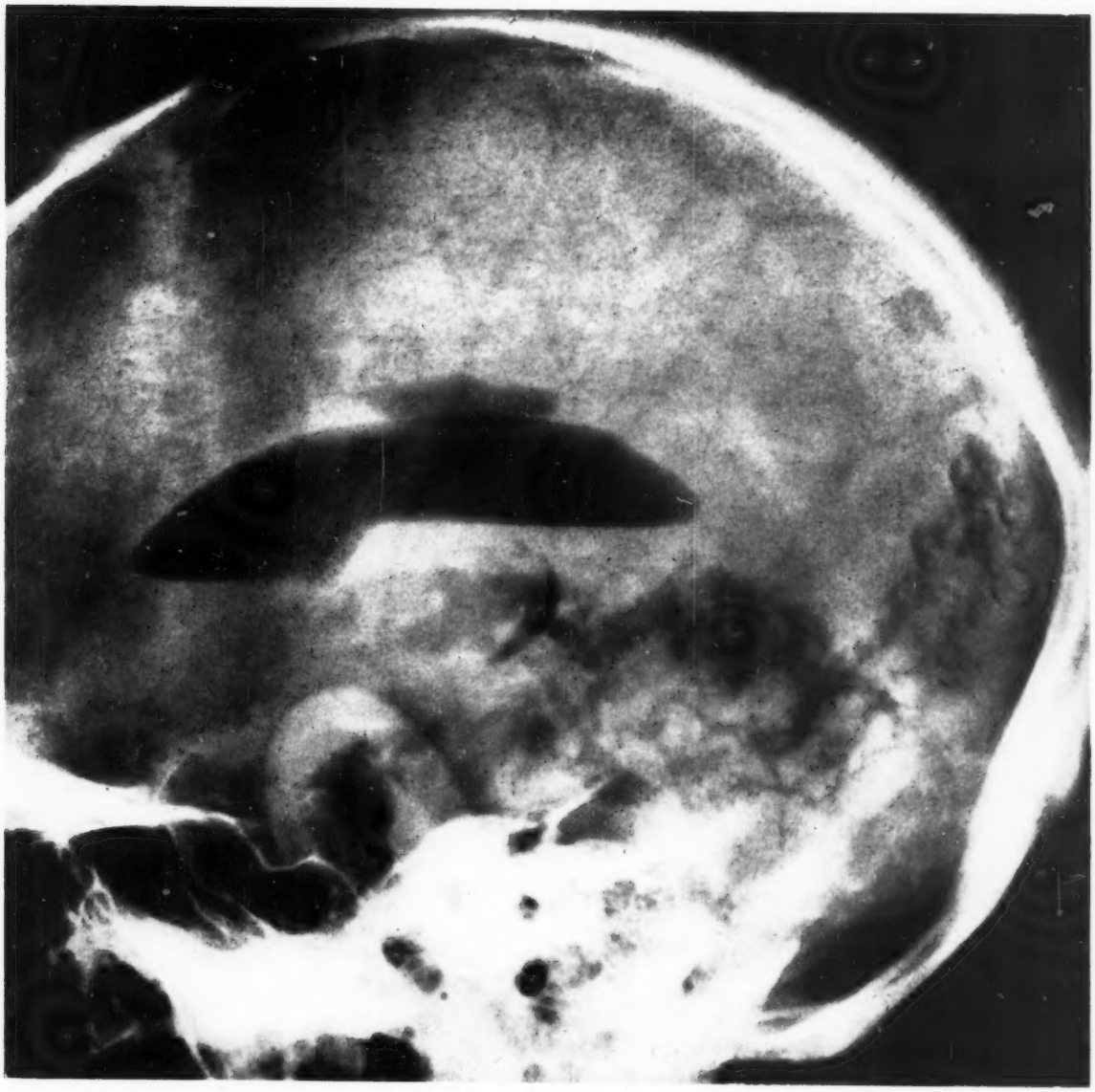

FIG. 5.—Filling of subarachnoid space over superior surface of cerebellum from the cisterna venæ magnæ cerebri.

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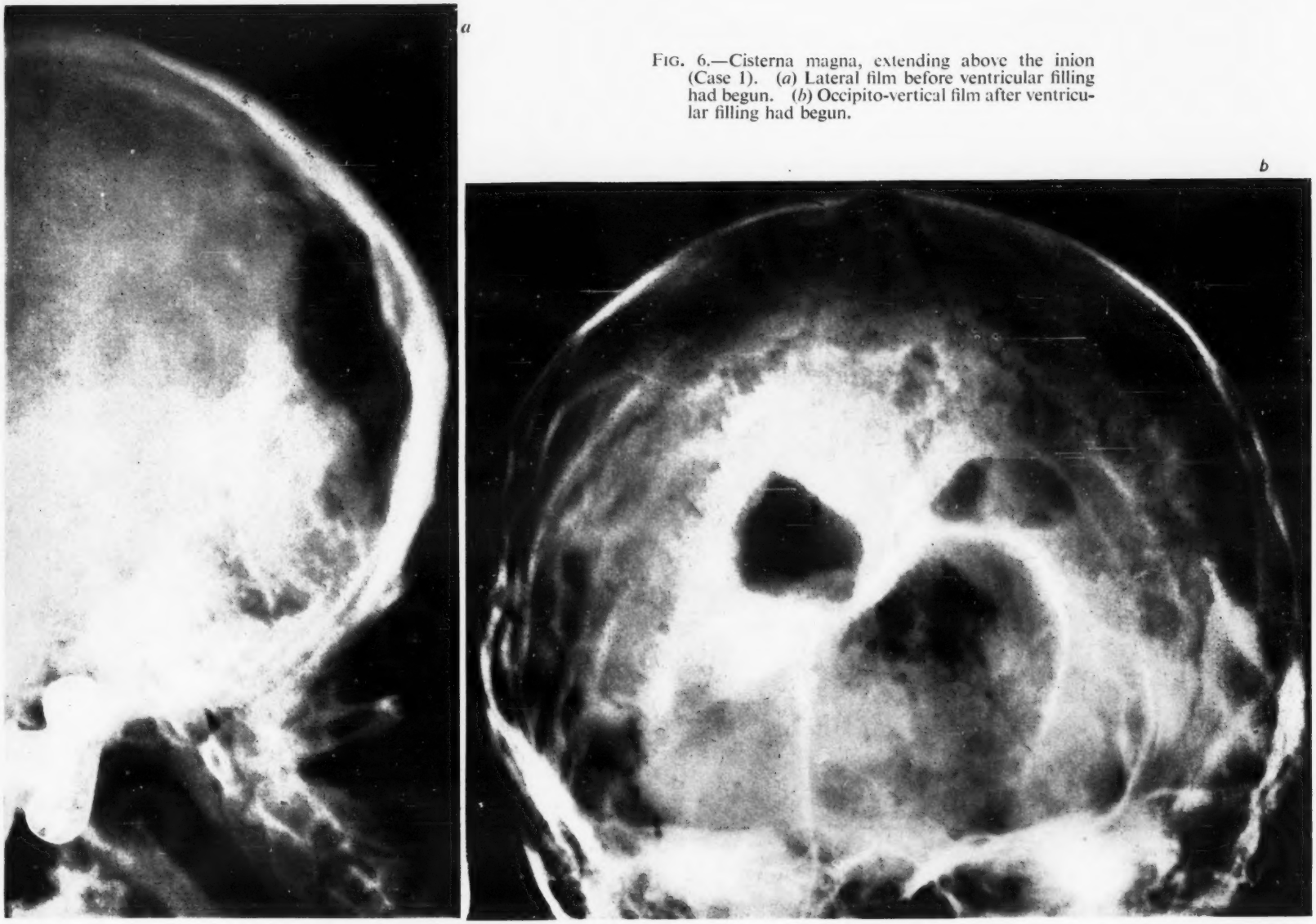

FIG. 6.—Cisterna magna, extending above the inion (Case 1). (*a*) Lateral film before ventricular filling had begun. (*b*) Occipito-vertical film after ventricular filling had begun.

FIG. 7.—Cisterna magna extending above the inion (Case 2). The ventricles and general subarachnoid space are also filled.

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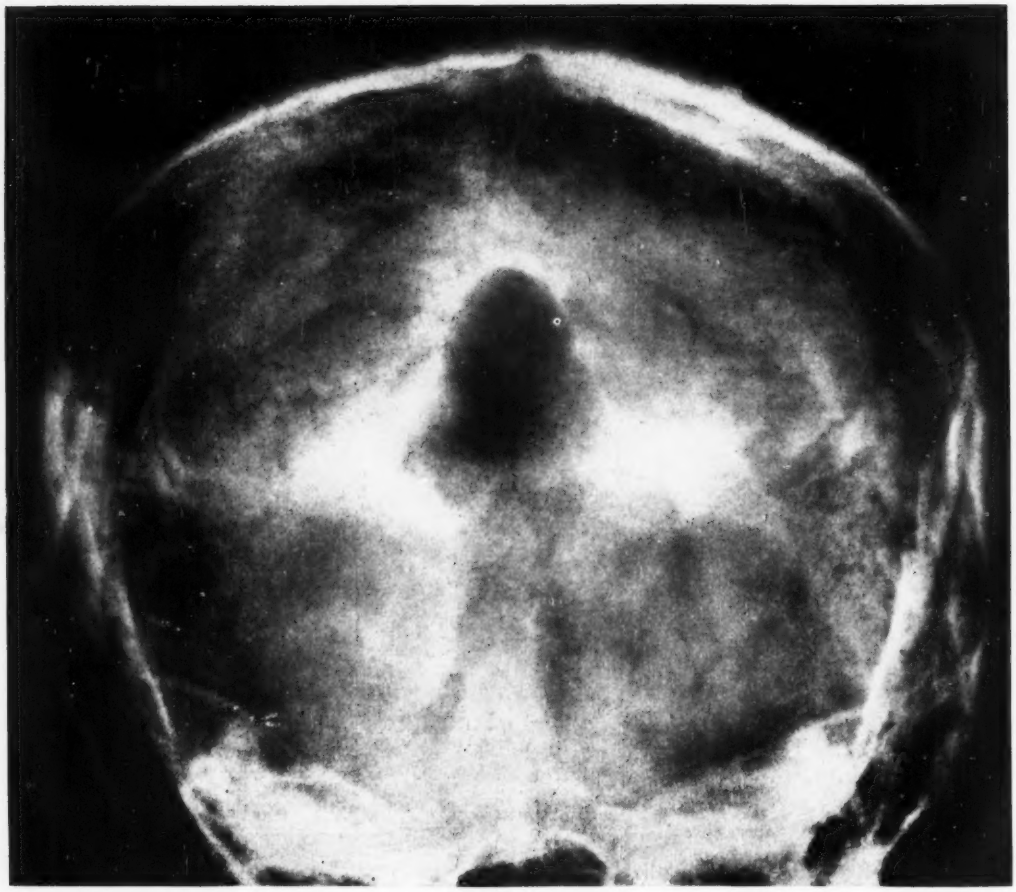


FIG. 8*a*

FIG. 8.—Cisterna magna extending higher than the inion (Case 3). (*a*) Occipito-vertical film, 7 c.cm. of gas outlining the apex of the cistern. (*b*) Lateral film at the end of filling. The large cistern outlines the vermis of the cerebellum, and (below) a cyst presenting between the cerebellar tonsils. The small interpeduncular cistern is shown, as well as the wide callosal and cingulate sulci.

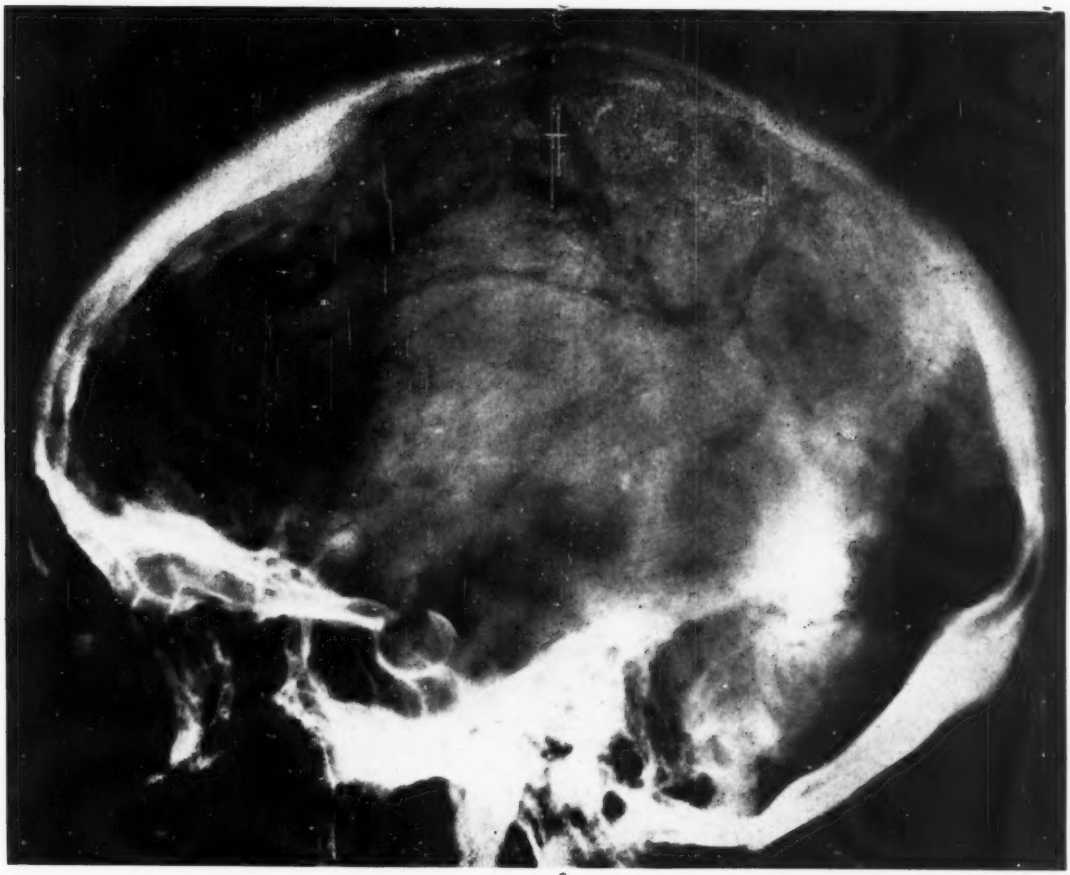


FIG. 8*b*

FIG. 9.—The dura mater seen from behind (Case 3). The occipital poles (over which the dura has been lacerated) are separated by a pocket of dura extending upwards from the posterior fossa.

FIG. 9

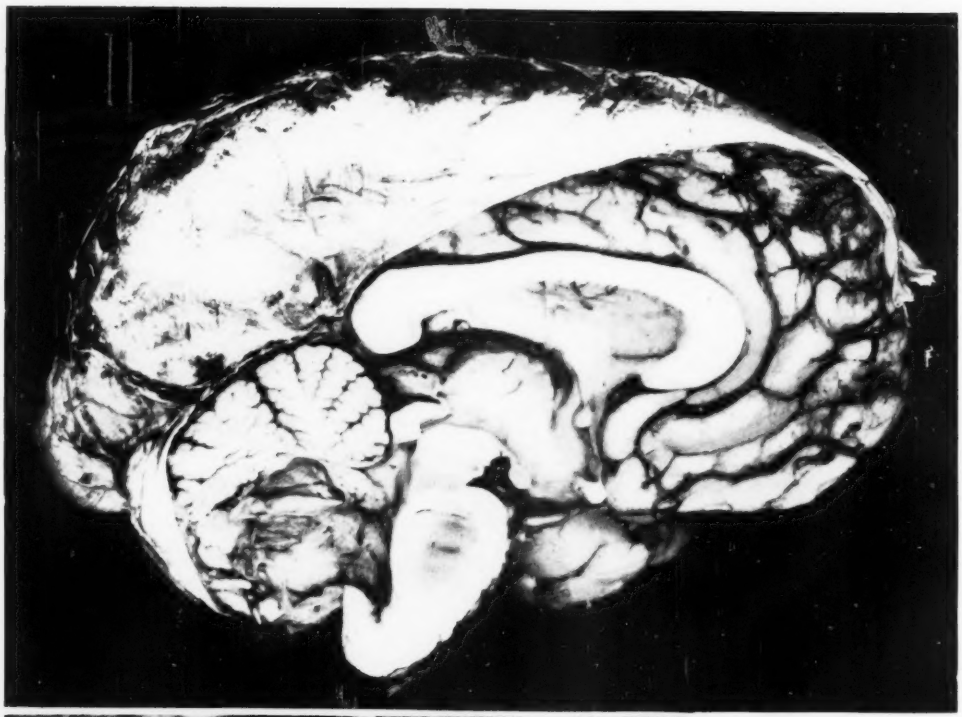
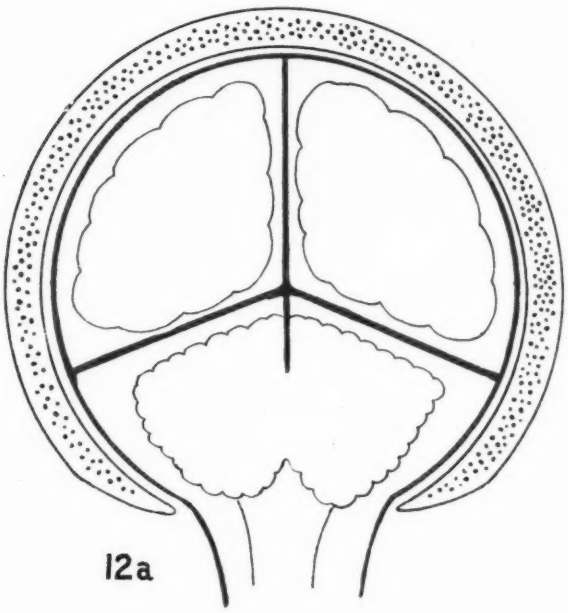
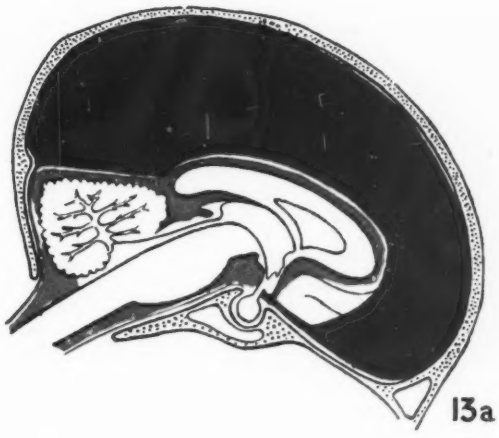
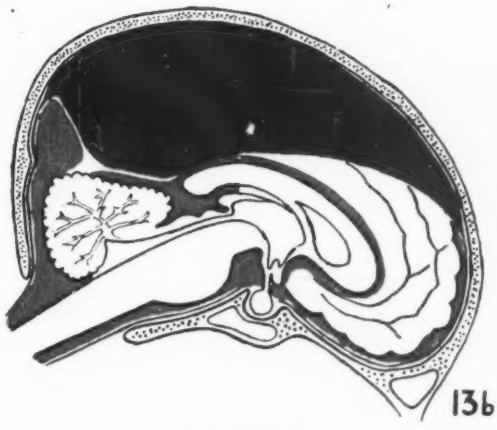


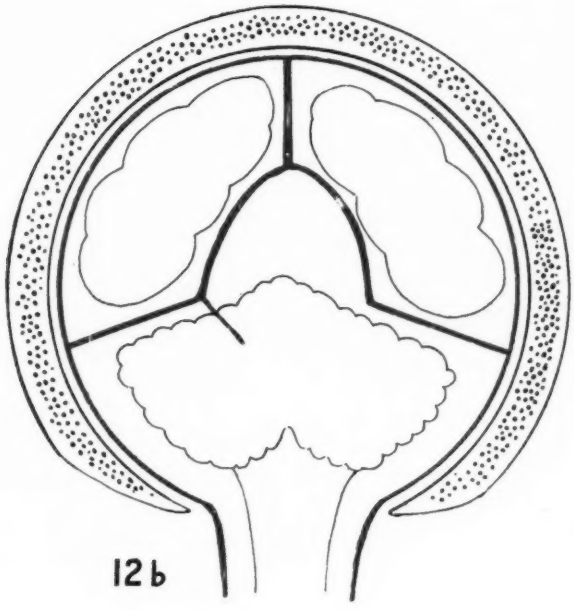
FIG. 10.—Sagittal section of brain with dura *in situ*. The left side of the dural pocket between the occipital lobes is seen. The falx cerebelli runs upwards to be attached to the left side of the mouth of the pocket. The anterior part of the falx is deformed. A small upper and larger lower cysts are seen replacing the lower part of the vermis.

FIG. 11.—Cyst wall projecting between separated cerebellar tonsils.









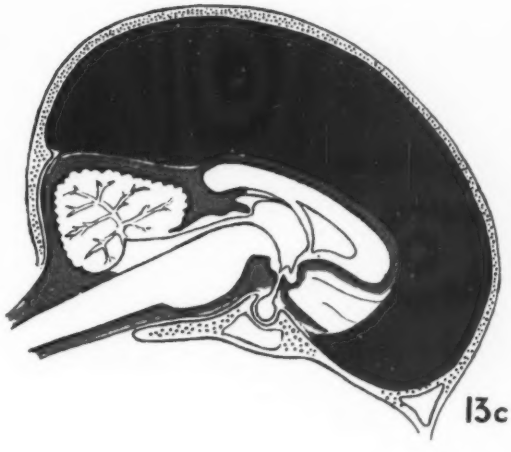


FIG. 12.—Comparison, in coronal sections, of normal and abnormal arrangements of the posterior part of the falx cerebri, the tentorium, and the falx cerebelli.

FIG. 13.—Comparison of normal arrangement of arachnoid and dura, with the abnormality which is the subject of this paper, and with that in which the cisterna magna is not delimited from the remainder of the subarachnoid space over the cerebellum.

[*Facing page* 48

study the dural arrangement which permitted such a surprising appearance.

Allied Abnormalities of Cisterna Magna, Tentorium, and Falx Cerebri

Case Report

A stout woman, 46 years of age, stated that for over twenty years she had suffered from attacks of headache which occurred during the afternoon once every two or three months. It was a severe ache, felt all over the head, and was sometimes associated with vomiting. The headache would disappear after sleep. There were no visual phenomena or bodily dysæsthesiæ.

Twenty months before admission to hospital she began to suffer from prolonged bouts of throbbing pain at the back of her head, which was relieved temporarily by analgesics. About two months later she was sometimes unsteady on her feet, with a variable tendency to stagger to the left side. Five weeks before admission she began to vomit when the headache was severe, on rising from recumbency, or after coughing had induced very severe headache. She was unable to stand unsupported. Lethargy increased to drowsiness, and on several occasions she could not be roused for periods of several hours. At other times she behaved in a peculiar uncontrolled fashion which was referred to as being hysterical.

The only abnormalities detected in the cranial nerves were as follows : upward rotation of the right eye was defective ; conjugate deviation to either side was poor—the right eye adducted poorly and the eyes tended to swing back towards the mid-line ; the left corner of the mouth moved slightly less than the right and the uvula was drawn slightly to the left side on articulation. There was no papillœdema. The motor power was good. In recumbency there was only slight inco-ordination of movement of all four limbs, with no unilateral preponderance. She would not attempt to walk when assisted into the upright posture, and when supported she tended to fall to the left side whether her eyes were open or shut. Her head was inclined to the right side, with the chin rotated slightly to the left. The reflexes and sensation were normal.

A diagnosis of neoplasm of the central portion of the cerebellum was made. It was thought probable that it involved the upper part of the vermis, with transmission of pressure to the third nuclei. However, the absence of papillœdema at this advanced stage was unexpected, and—chiefly because of this—investigation was undertaken. The pressure of the cerebrospinal fluid was 140 mm. and the response to jugular compression was normal. The fluid was clear and colourless. It contained 1 large mononuclear cell in 3 c.mm. The protein content was 50 mg. per 100 c.cm. without increase in the globulin fraction. The colloidal gold curve was normal. The Wassermann reaction was normal in blood and cerebrospinal fluid.

Radiographs of the skull disclosed no abnormality. The first postero-anterior film during encephalography showed an unusual collection of gas in the mid-line above the level of the inion (Fig. 8). Lateral films showed it to lie immediately in front of the inner table of the interparietal portion of the occipital bone. The shadow at the level of the inion measured 3·6 cm. in width, and 2 cm. in depth. As filling continued, the collection of gas extended downwards towards the foramen magnum. There was little doubt that this shadow represented the cisterna magna, very much larger than usual and extending above the internal occipital protuberance almost half-way to the lambda, with its apex above the usual level of the tentorium. There appeared to be two possibilities—first, that there was a hiatus in the posterior medial portion of the tentorium through which a cul-de-sac of arachnoid passed before being reflected back on to the cerebellum, or secondly, an abnormal conformation of the dura existed without an actual break in continuity. The posterior surface of the vermis was well outlined and the width of the shadow of gas suggested that the cerebellum was not enlarged. Below, the cistern did not extend forwards to the region of the foramen of Magendie, being interrupted by a globular projection. This extended into the foramen magnum, forming posteriorly an unusually defined and acute angle with the shadow of the inferior surface of the cerebellum. It was taken to represent the depressed cerebellar tonsils. Having filled the cisterna magna, gas began to pass upwards anterior to the medulla and pons into the interpeduncular and ambient cisterns. No manœuvre secured ventricular filling. The pontine and interpeduncular cisterns were small, and the upper surface of the pons appeared to be higher than usual (Fig. 8b). The floor of the third ventricle was slightly depressed. The callosal and cingulate sulci appeared higher than normal, and were wider than usual. It was believed that the appearance suggested the presence of a tumour in the posterior cranial fossa, the absence of ventricular filling being ascribed to blockage of the foramen of Magendie. For a short period the patient's clinical state improved and exploration of the posterior fossa was projected, although it was believed that little prospect of cure existed. However, she passed once again into a drowsy stage which on this occasion deepened to coma, and she died before operation could be performed.

At post-mortem examination the calvarium was separated from the dura and removed. This exposed a globular projection of dura mater between the occipital lobes, the dura being continuous with that over the cerebellar hemispheres below and laterally with that over the occipital lobes (Fig. 9). Veins, larger on the left side, coursed along each side of the convexity, from the longitudinal sinus at its apex to the transverse sinuses below on each side. Dissection showed the bulge to be the posterior wall of a dural pocket, the mouth of which opened below, through a hiatus in the tentorial shelf, into the posterior fossa (Fig. 10). The two lateral walls, meeting anteriorly, appeared to be formed by splitting of the posterior inferior portion of the falx cerebri into two layers which, below, turned sharply laterally to become continuous with the tentorium (Fig. 12b). The falx cerebelli was well developed. Above, its anterior edge was attached at the meeting point of the tentorium, the falx, and its two derivative layers (Figs. 10 and 12). Behind this point

it veered to the left, to be attached to the lateral wall of the pocket as it turned to become the tentorial dura. The dural pocket contained a cul-de-sac of arachnoid of the cisterna magna. The posterior part of this membranous pocket was continuous with the arachnoid of the cisterna magna, the anterior wall with that over the superior surface of the cerebellum to which it became firmly applied. The veins which normally meet at the torcula coursed along the angles of the dural sac. The straight sinus divided into three channels, one running upwards to the superior sagittal sinus and one on each side to the transverse sinuses (Fig. 10). The sagittal sinus divided into two main and several smaller trunks which passed downwards to the transverse sinuses (Figs. 9 and 10). The anterior part of the falx cerebri was also malformed. Its anterior edge passed forwards and upwards, above the splenium of the corpus callosum, to reach the dura over the cerebral hemispheres above the genu of the corpus callosum (Fig. 10). There was no dura between the medial surfaces of the frontal lobes.

Thus, the dural membrane shows two unusual anomalies together with a very large cisterna magna. Fig. 13 illustrates diagrammatically the normal and abnormal arrangements of the dura and cisterna magna, and shows also the anomaly previously described in which absence of occlusion of the upper part of the cisterna magna allows gas to rise directly to the superior surface of the cerebellum (see Fig. 4). Although pathological confirmation is lacking, it is probable that a similar defect exists in the posterior part of the dura whenever the cisterna magna extends above the inion, as in the two further cases mentioned. It is not known whether the anteriorly placed defect was present in the other instances. It is possible that the dural defect might exist without abnormality of the cisterna magna, in which case the anomaly would not be recognized during encephalography.

The dural pocket and neighbouring occipital lobes have a stable appearance which suggested a life-long existence. Microscopically, the membrane resembled normal dura although it contained a number of dilated venules, the distension being probably due to terminal venous congestion. There were no indications of preceding inflammation in the sections. Thus, a developmental lesion seems to be the most likely explanation. If this was due to maldevelopment, two possibilities arise : injury (inflammatory, vascular or traumatic) with subsequent repair causing an unusual pattern ; or genetic influences. It is possible that future observations may provide evidence to decide which is the cause ; for example, the presence of a familial incidence would favour a genetic cause.

Account of Coincident Cyst in Vermis

When, during removal, the dura and arachnoid were incised transversely at the level of the foramen magnum, a translucent membrane, enclosing clear fluid, was seen to project between the cerebellar tonsils (Fig. 11). There were no adhesions between this membrane and the overlying arachnoid. Median section of the brain showed it to be part of the thin wall of the lower of two cysts which occupied most of the lower part of the vermis and pressed into the lateral lobes of the cerebellum on each side (Fig. 10). The upper cyst reached the medullary body of the cerebellum above, and anteriorly was separated from the roof of the lower part of the fourth ventricle by a thin layer of cerebellar tissue apparently representing the nodule. Posteriorly the tuber and pyramid of the vermis were seen and appeared to be compressed. The uvula had largely disappeared, being represented only by a little tissue. The foramen of Magendie was patent and higher than normal, at much the same level as the double wall between the two cysts. Small vascular tufts, continuous with the choroid plexus of the fourth ventricle, ran into small vessels which dispersed over the anterior upper part of the wall of the lower loculus. The arachnoid of the cisterna magna was not connected with the cyst. It was apparent that the shadow in the encephalograms which was taken to represent the cerebellar tonsils was, in reality, due to the lower part of the cyst projecting between the cerebellar tonsils. The wall was composed of a thin layer of delicate fibrous tissue with an internal lining of a single layer of cuboidal cells. Some small vessels ran between the cyst wall and the atrophied cerebellar tissue in its neighbourhood. Neurons and glia were seen in the remnants of vermis applied to the wall of the cyst. The cuboidal cells of the walls of the cyst were similar in appearance to normal ependymal cells. There was no arachnoidal thickening, and the cyst was not connected with the arachnoid. The microscopical appearance, the position of the cyst, the absence of arachnoidal abnormality, and the relationship of the choroid plexus, raises the possibility of an ependymal origin. Such cysts are rare, but a number having a similar position have been described, notably by Zehnder (1938). He believed the cysts to be similar in type and origin to others which he described in the Sylvian fissure and between the cerebral hemispheres, and ascribed an arachnoidal origin. Most were lined by a single layer of cuboidal cells, but one had several layers of cells with an internal layer of pigment-storing ciliated epithelium.

Structurally, these cysts are unlike the condition described by Horrax (1924) under the title " Generalized Cisternal Arachnoiditis," although each may produce " the localizing features of a cerebellar lesion simulating tumour." In the latter

group of cases there was " arachnoid thickening of the basilar cisternæ as well as that overlying the cerebellum." Operative exploration disclosed a greatly dilated posterior cistern with thickened arachnoid membrane containing pent-up cerebrospinal fluid. The foramen of Magendie was blocked, causing internal hydrocephalus. The condition was believed to be an inflammatory one.

Allen and Corkill (1937) described a number of cases in which arachnoidal cysts occupied the cisterna magna. Such deep penetration of the cerebellum was not apparent in their cases as in that pictured by Zehnder, and that here described. Their cases appeared to be similar to those described by Horrax.

Shryock and Alexander (1943) reported the clinical and pathological findings in a fourteen year old girl who had a number of developmental anomalies. There was evidence of mild cerebellar dysfunction eight months before her death from peritonitis following volvulus. They describe the fourth ventricle as being enlarged at the expense of the substance of the cerebellar vermis and continuous with a cyst which extended caudad between the cerebellar tonsils and laterally on each side of the medulla oblongata. The cyst was bounded by a membrane which was continuous with the ependyma of the rhomboid fossa internally, and with the arachnoid covering the cerebellum externally. Microscopically the lining consisted of ependyma and nervous tissue. There were two small, laterally placed cysts, " the significance of which was not clear." They collected eight other cases in the literature, mostly young, but one aged 59 years. Five of the eight cases presented symptoms suggesting cerebellar disease. Nystagmus was noted in three cases, positive Rhomberg's sign in two, and hypotonia in one. Gradual increase in the size of the head was mentioned in four instances. Enlargement of the third and lateral ventricles was noted in five cases, of the third alone in another. In three, the foramina of Luschka and Magendie were obstructed, in one the foramina of Luschka were patent. Four died following surgery. There was considerable variation in the degree of deformity of the cerebellar vermis. Some authors thought that parts of the vermis had disappeared, others that all parts were present, even if rudimentary.

Following Dandy they believe the condition to be due to obstruction to the foramina of Magendie and Luschka by inflammatory processes, or to their failure to develop ; or perhaps to tardy opening of the foramina. This is thought to lead to dilatation of the fourth ventricle, which during the fourth month of intra-uterine life encroaches upon the embryonic structures which are fusing to form the posterior portion of the cerebellar vermis, causing them to remain rudimentary. Opening of the foramina might occur at a later time, allowing circulation of the cerebrospinal fluid and cessation of dilatation.

A case fully reported by Sahs (1941) and more clearly described than most of the other pathological conditions in this region is included in Shryock and Alexander's collected series. This case is much more suggestive of agenesis of the vermis without primary obstruction to the foramina of Magendie and Luschka. Had the anterior wall of the cyst disappeared in the case recorded here, the appearance would have been very similar to that described by Shryock and Alexander. In this case the association with other developmental defects of the dura favours a developmental cause for the cyst in the posterior fossa. However, the advanced age at which symptoms appeared suggests that the cyst developed late in life, although its seeds might have been due to factors active during intra-uterine growth.

Thus inflammatory, traumatic, and congenital causes have been evoked to explain the presence of cysts presenting in the cisterna magna, some associated with atrophy of the vermis. It is probable that there is more than one type of cyst presenting in this region. Cysts replacing the lower median part of the vermis may arise from ependyma, perhaps during intra-uterine growth, perhaps later in life, and they probably constitute a different group from the arachnoidal cysts which commence in the cisterna magna. Disappearance of parts of the cyst wall would result in an appearance similar to that which has been thought to be due to maldevelopment of the vermis, but it is not known whether this occurs.

Summary

The normal arrangement of the cisterna magna is described.

Four variations are recorded which owe their recognition to encephalography. Each calls for modification of encephalographic technique if ventricular filling is to be attained.

A large cisterna magna, seen during encephalography to extend above the inion, was associated with abnormalities of falx cerebri and tentorium, which are considered to be of developmental origin.

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CRUSHING INJURIES TO THE SKULL: CLINICAL AND EXPERIMENTAL OBSERVATIONS

BY

W. RITCHIE RUSSELL and F. SCHILLER

From the Department of Neurology and the Accident Service, Radcliffe Infirmary, Oxford

Severe crushing injuries of the head are often fatal, but in those patients who survive this form of injury the absence or slight degree of concussion is usually a striking feature of the clinical picture. Even though the skull may be fractured and the cranial nerves injured, the patient often remains fully conscious. This clinical observation led one of us (W.R.R.) with Denny-Brown (1941) to investigate experimentally the mechanism of cerebral concussion, and we found, as might be expected from clinical experience, that concussion is more readily produced by a blow when the head is free to move and not fixed. In most cases of accidental head injury the head is subjected to a sudden change of momentum which causes the shearing stresses in the brain which have been analysed by Holbourn (1943), and so brilliantly demonstrated experimentally by Pudenz and Shelden (1946). It seems clear that the common retention of consciousness with crushing injuries of the skull is due to the absence of any sudden change of momentum with an injury of this nature.

Compression of the skull beyond a certain degree will, however, cause loss of consciousness and brain damage by cerebral compression. The term *compression concussion* has been used to denote this form of injury (Denny-Brown and Russell, 1941).

Case Records

Case 1.—J. O'B., a miner, aged 49, was admitted to the Royal Infirmary, Edinburgh, on Jan. 1, 1933, shortly after an accident. He was working in a coal seam 26 inches high when a fall of rock pinned his head to the ground (lateral compression). He remained fully conscious but when released by other workers he was bleeding from the nose and right ear. When examined next day he was fully conscious, and there was little headache. There was a bruise in the left frontal region and extensive subconjunctival hæmorrhage in the right eye. He reported having swallowed a lot of blood from his nose: there was blood in the right ear and right facial weakness. Radiographs of the skull failed to show a fracture. By Jan. 29, 1933, there was complete right facial paralysis and complete right sixth-nerve palsy. He was discharged home on Feb. 4, 1933. The cranial nerve palsies recovered slowly, but on Dec. 24, 1943, he fell in an attack of vertigo and fractured the neck of his left femur. In February, 1935, his health was satisfactory, and he was planning to start light work.

Case 2.—T. L., a railway carriage examiner, aged 31, was admitted to the Royal Infirmary, Edinburgh, on July 24, 1933, after an accident in which his head had been crushed between two railway carriages. He remembered all details of the accident and after release was able to walk for five minutes to a house. There was bleeding from the nose and both ears. He was conscious but very shocked on admission to hospital. When examined on July 25, 1933, he was fully conscious, but had severe headache and marked neck rigidity. The left pupil was larger than the right and there was complete left sixth-nerve paralysis. Radiological examination revealed a fissure fracture in the right fronto-temporal region. On Aug. 1, 1933, the cerebrospinal fluid pressure was 100 mm. of water and the fluid was deeply blood-stained (33,000 red cells per c.mm.) and on standing the supernatant fluid was bright yellow. The white cell count was 314 per c.mm. (15 per cent. polymorphs). Following lumbar puncture he had a rigor and high fever at night for five days; thereafter he made a gradual recovery and was discharged home on Aug. 17, 1933.

Case 3.—A. C., a labourer, aged 43, had his head and left leg pinned down by heavy oil drums sliding down from a pile. He did not lose consciousness, and he said afterwards that he was most concerned with the immediate pain in his crushed leg, and he shouted for help to be released from the drums as he was unable to extricate himself. He was bleeding from his left ear which, from having a slight previous defect in hearing, became completely deaf. There was a transient left sixth-nerve weakness and an almost complete left facial palsy which was still present one month after the accident. Only special oblique radiograph showed a fracture of

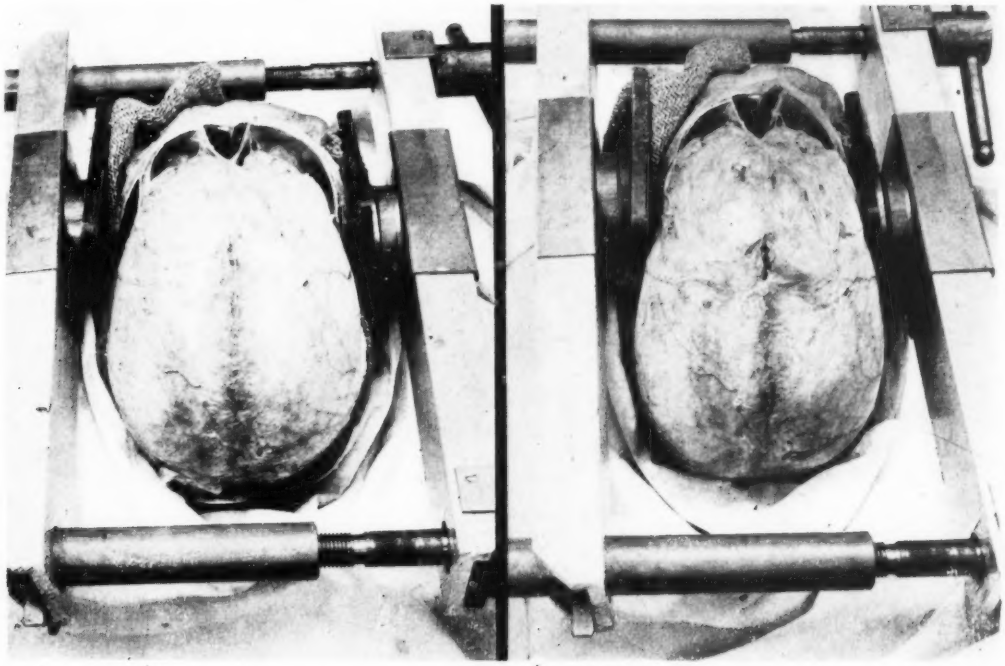

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FIG. 1a.—The vice gripping the skull in a rather anterior transverse diameter, before applying pressure.

FIG. 1b.—Note bilateral narrowing and antero-posterior elongation of skull after crushing, and moderate deformity of brain (experiment VIII).

FIG. 2.—Transverse crush, rather oblique. Note typical avulsion of petrous bone, which has been forced medially and rotated backwards. Other fractures running into right orbital fissure and left posterior fossa (experiment IX). (The sides have been reversed by the camera.)

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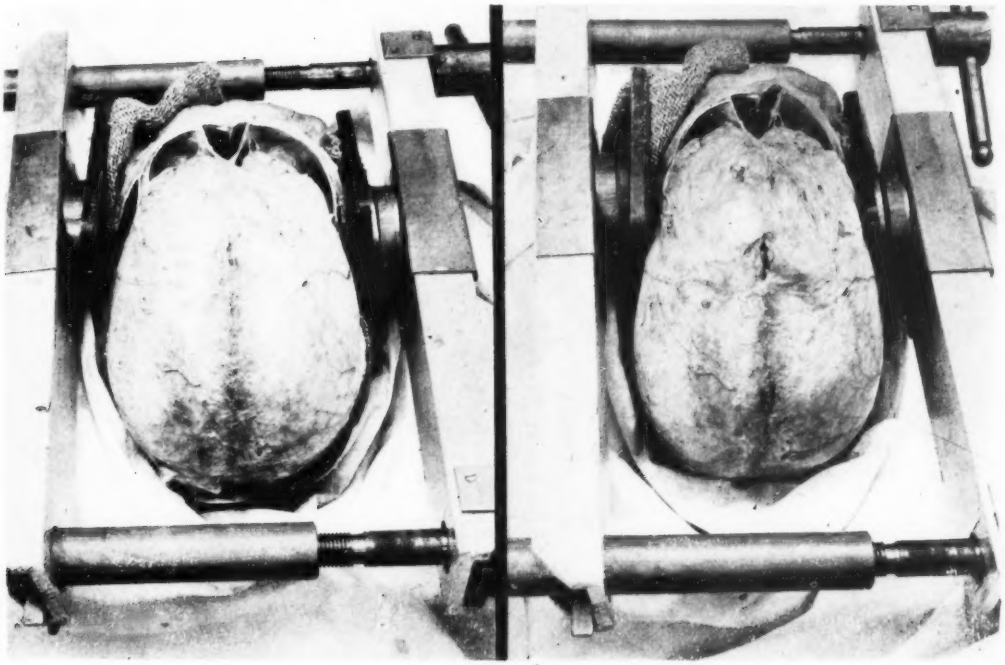

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FIG. 1a.—The vice gripping the skull in a rather anterior transverse diameter, before applying pressure.

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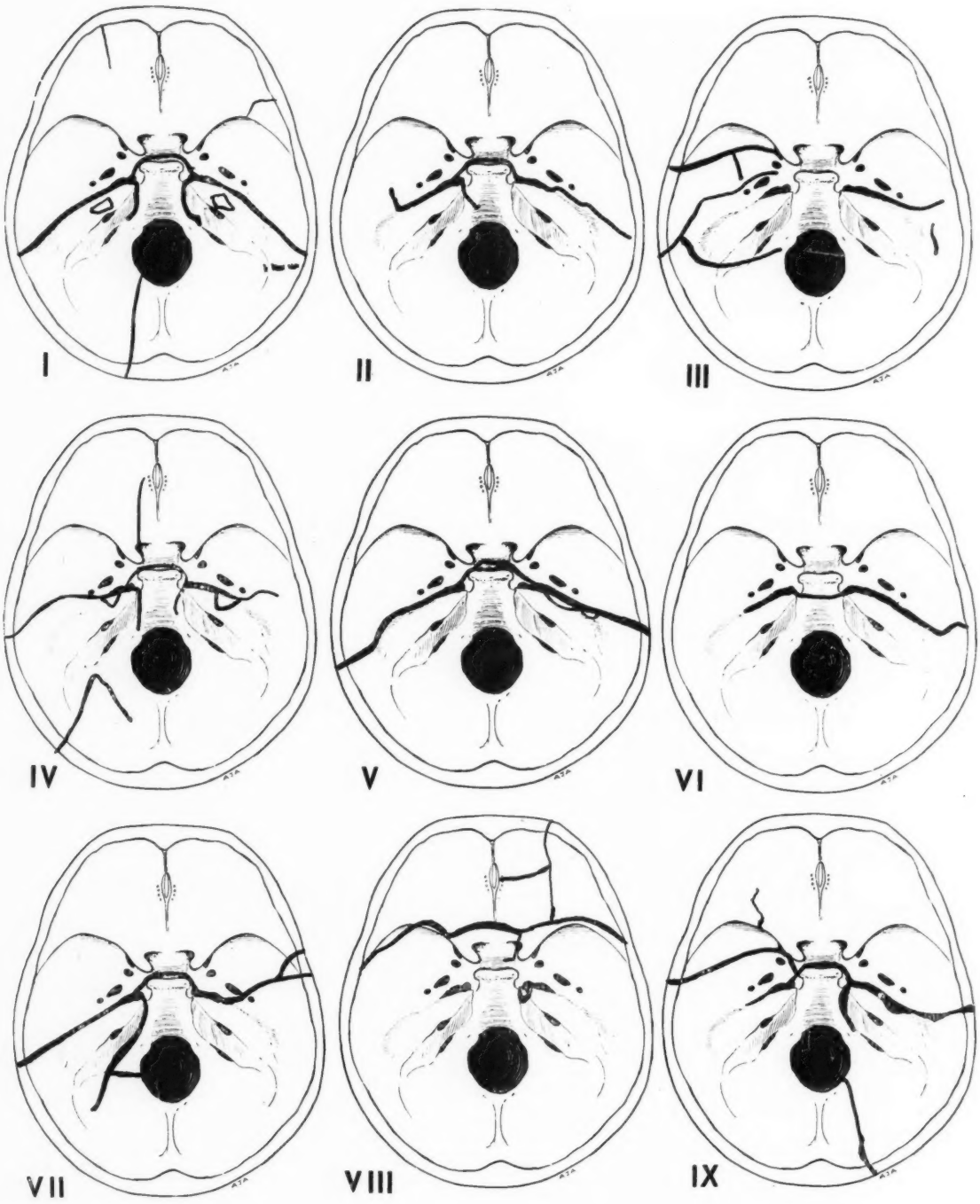

FIG. 3.—Fracture lines resulting from bilateral application of vice (experiments I to IX).

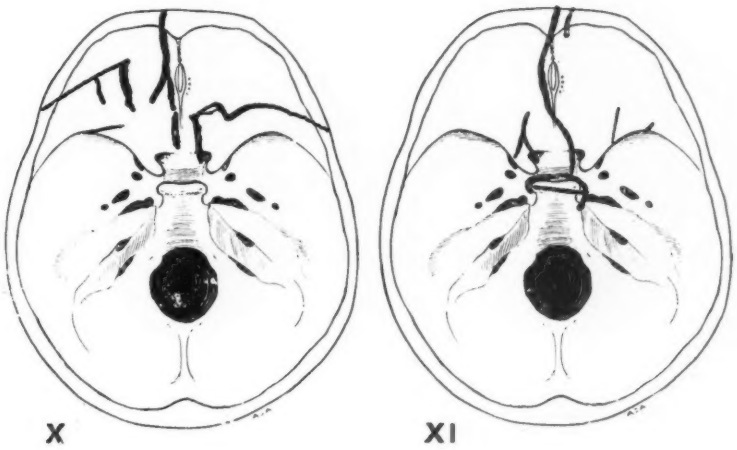

FIG. 4.—Fracture lines resulting from antero-posterior application of vice (experiments X and XI).

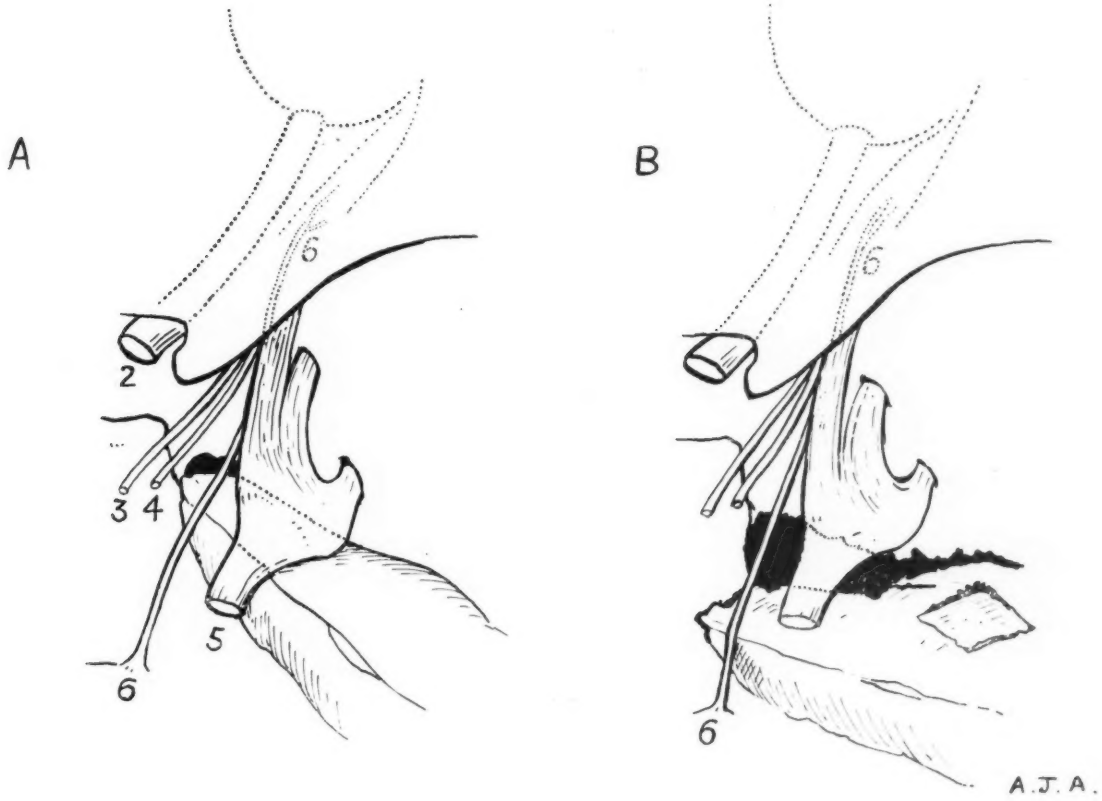

FIG. 5.—Schematic drawing of third, fourth, fifth, and sixth cranial nerves in relation to petrous apex, presuming that dura, cavernous sinus, internal carotid, artery, etc., have been dissected away.

(A) shows normal position, (B) stretching of sixth (and fifth) nerves across the gap, produced by crushing and avulsion of petrous bone ; the more medially placed third and fourth nerves remain intact. Note also the dislodged and fractured tegmen tympani.

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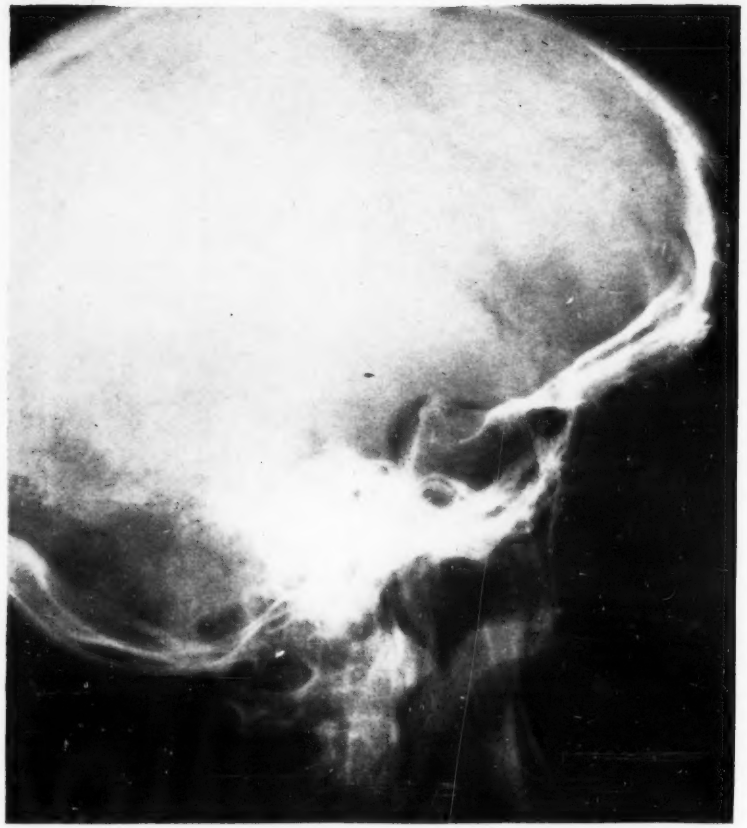

FIG. 6.—Experimental crush (experiment VI, see Fig. 3). Note aerocele in cisternæ chiasmatis and pontis. A fine fissure rising from petrous bone is the only visible evidence of the fracture shown in Fig. 2.

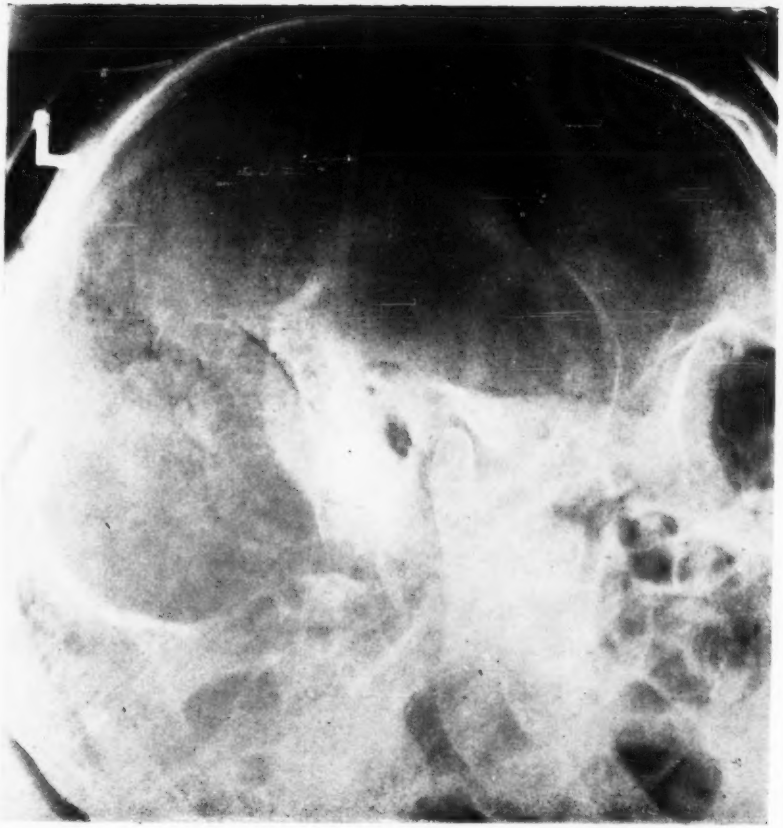

FIG. 7.—Oblique lateral projection, showing fracture running into petro-mastoid (Case 3).

the left petrous bone involving the mastoid air cells (Fig. 7). The patient would have been able to resume work within three weeks, but for the fractured leg.

Case 4.—When 22 years of age J. R., a miner, was crushed between two hutches in the mine. He remembers all details of the injury and apparently the crush was bitemporal in direction. There was bleeding from both nostrils and the right ear. When examined seventeen years later (March 11, 1935) he was in fair health but had suffered from headaches at frequent intervals ever since the injury.

Case 5.—J. McN., aged 63, was admitted to the Royal Infirmary, Edinburgh, on Dec. 2, 1936, shortly after an accident. While he was standing between a motor lorry and a wall the lorry moved backwards and pinned his head against the wall. There was no loss of consciousness, and he remembers clearly the acute pain caused by the injury. Blood poured from his right ear, nose, and mouth. On the following day he developed complete left facial paralysis and there was slight deafness of both ears. There was effusion around the right eye with subconjunctival hæmorrhage. He had severe headaches for twenty-four hours. *X*-ray examination demonstrated a fracture in the right temporal bone.

He returned home on Jan. 5, 1937. When seen again on Sept. 6, 1937, he was free from symptoms and the facial paralysis had recovered.

Case 6.—W. G., a pit-boy, aged 15, was caught between two hutches in the mine on Oct. 11, 1937. Consciousness was not disturbed, and he was able to jump aside when the hutches separated. He remembers the severe pain of the crush, and blood poured from both ears and both nostrils. He was admitted to the Royal Infirmary, Edinburgh, the same day. There was pain in the head for a few days only, but radiographs revealed a vertical fracture involving the right parietal, squamous and petrous portions of the temporal bone. There was slight impairment of the sense of smell on the right side, and left facial weakness. He made a quick recovery, and when re-examined on Feb. 7, 1938, he felt quite fit.

Case 7.—J. T., a pit-boy, aged 14½ years, was crushed between hutches on Oct. 11, 1937. He remembers all details of the injury, but was reported to be dazed when admitted to the Royal Infirmary, Edinburgh, a few hours later. There was no *x*-ray evidence of fracture, but blood escaped from both ears and the nose. Five days later stereoscopic radiographs with the occipito-mental projection failed to show any fracture of the base of the skull. On Oct. 19, 1937, he was feeling fairly well but had diplopia. The left pupil was larger than the right, and reacted normally to light and convergence. The right pupil was inactive to light but contracted slightly on convergence. There was slight limitation of the outward movement of the left eye. On Jan. 5, 1938, the diplopia had recovered and the pupils were normal: he felt quite well and ready to resume work.

Case 8.—E. M., aged 29, while cycling was caught between two motor vehicles and his head was crushed. So horrible did the accident look that he was reported dead in the evening paper of Sept. 29, 1947. But when admitted to the Radcliffe Infirmary, Oxford, he was found to be only moderately concussed, and he regained full consciousness a few hours after the accident.

There was bleeding from the left ear, bilateral deafness of a middle-ear type, bilateral external rectus and bilateral facial palsy, and complete anæsthesia and masticatory paralysis on the right side of the face. There was dysarthria and dysphagia, but no evidence of abnormality of the long cerebrospinal tracts. Radiographs showed a fracture running into the left middle fossa, and an ærocele filling the interpeduncular cisterna.

The hearing in both ears returned (with a scarred drum on the left side). The dysphagia subsided. But he remained somewhat dysarthric and much troubled by the lesions of the right fifth nerve and of both sixth and both seventh nerves.

Case 9.—Rfmn. P., aged 21, was on Dec. 6, 1941, crushed between an army lorry and a girder in a garage. He remembers the impact but nothing more for about twenty minutes, when he remembers being in an ambulance. On recovering consciousness he was found to have extreme dysarthria of a cerebellar type with ataxia of the limbs. The pupils were eccentric, being nearer the nasal edge of the cornea. They were also not quite circular, and there was marked hippus. No other abnormality was noted. *X*-ray examination revealed an extensive comminuted fracture of the left parietal bone, 10 by 5 cm. in size. Eighteen months later his speech was still indistinct. He complained of headaches, irritability, and periods of depression. He had been obliged to give up several jobs.

Case 10.—Gnr. S., aged 29, was on Nov. 10, 1941, examining a gun tyre when the vehicle moved and passed over his head, pinning him to the ground. He remained fully conscious, but was unable to speak, and drummed the ground with his feet to attract attention. There was bleeding from the right nostril for an hour and some headache for twenty-four hours. In hospital he was found to have a complete ophthalmoplegia and blindness of the right eye, with anæsthesia in the distribution of the right supraorbital nerve. He remained fully conscious. The right clavicle was fractured.

X-ray examination revealed fractures of the roof of the right orbit, the right optic foramen, and of the greater wing of the sphenoid.

By April 30, 1942, both the vision in the right eye and the ocular movements had recovered. The right pupil was, however, smaller than the left and inactive to light. As far as the head injury was concerned he had made a good recovery.

Case 11.—Gnr. A. F., aged 24, was on Feb. 11, 1941, travelling in a lorry when it overturned and he was crushed by 100-lb. shells it was conveying. Though there was no loss of consciousness and no amnesia, there was bleeding from the nose and weakness of the left sixth and seventh cranial nerves. The left pupil was

smaller than the right and there was slight left deafness. He developed pulsating exophthalmos of the left eye, which was cured by ligation of the internal carotid artery first in the neck and later within the skull. Glaucoma of the left eye developed with complete loss of vision. *X*-ray examination failed to reveal any fracture. A year after the injury he was able to resume light manual work.

Case 12.—2/Lt. S., aged 20, had his head crushed below a Morris 8-h.p. motor car when the jack slipped. The rear axle pinned his head to the ground. He remained fully conscious while a friend lifted the car, and he was then able to get out and to stand up with blood pouring from his nose and right ear and from a cut on the left forehead. He noticed double vision while being taken to hospital. There was slight weakness of the right lateral rectus muscle, depression of the right corneal reflex, right facial paresis, and slight right deafness. Radiographs revealed a fissure fracture of the anterior part of the left squamous temporal bone which ran vertically upwards to the squamo-parietal junction, and downward into the base of the skull.

He made a good recovery and returned to duty two months after the injury.

Case 13.—Spr. S., aged 28, was on July 1, 1941, working under a truck when the jack slipped, and his head was pinned between the front axle and the ground. He was rendered deeply unconscious and had amnesia for fifteen days. There was bleeding from left parietal and right occipital wounds, but none from the nose or ears. The cerebrospinal fluid fourteen hours after the injury contained blood; the pressure was 180 mm. of water. The right pupil was larger than the left, and the left arm and leg were slightly spastic with a left extensor plantar response.

X-ray examination revealed no fracture of the skull. Some weakness of the left side persisted, but he made a fair recovery and resumed light work nine months later.

Case 14.—Gnr. M., aged 30, was on May 6, 1942, caught between two heavy motor vehicles moving very slowly. He did not lose consciousness at any time, but a bolt on one of the vehicles caused a depressed fracture of the right temporal bone. This was operated on the same day: the dura was intact. There was also a cut in the left occipital region. The only abnormal physical signs were nystagmus and the right pupil was larger than the left. He made a good recovery apart from some headaches reported on a follow-up report dated Oct. 13, 1943.

Case 15.—Pte. O.M., aged 20, overturned a truck he was driving on Feb. 26, 1942. While crawling out the truck settled on his head. There was no loss of consciousness or amnesia. Radiographs revealed a depressed fracture in the left parieto-temporal region.

He made a good recovery, and a year later was reported free from symptoms but serving a sentence in prison.

Discussion of Clinical Cases

The cause of the crushing injury in these fifteen cases was as follows:

	Cases
Head caught between hutches	3
Head crushed by fall of rock in mine	1
Crush between railway carriages	1
Crush between backing lorry and wall	2
Crush between 2 motor vehicles	2
Crush under axle of motor vehicle	2
Crush under overturned lorry	1
Crush under oil drums	1
Crush under several 100-lb. shells	1
Crush under gun-wheel	1

The signs of skull injury were:

X-ray evidence of fracture	10
Bleeding from the ears	9
bilateral	3
Bleeding from the nose	9

Fourteen of the fifteen cases showed clinical or *x*-ray evidence of skull fracture. Nevertheless the absence of concussion was a marked feature of most cases. Indeed all remained fully conscious without amnesia except three of the fifteen in which there was amnesia for twenty minutes, a few hours, and fifteen days respectively.

All except three cases showed cranial nerve involvement as follows:

	Cases
Second cranial nerve	2 (one optic chiasm)
Fifth cranial nerve	3 (upper division)
Sixth cranial nerve	8 (bilateral in one)
Pupillary changes	6
Ophthalmoplegia	1
Deafness	5 (bilateral in two)
Dysarthria	2

One patient developed a carotico-cavernous aneurysm, one a severe mid-brain syndrome, and one an ærocele. In two cases sub-arachnoid hæmorrhage was demonstrated.

The clinical features are therefore quite striking, for there is commonly clear evidence of fracture of the base of the skull and injury to cranial nerves without any of the loss of consciousness or concussion which so constantly accompanies the common forms of accidental head injury.

Experimental Crush Injuries

As the clinical features of crushing injuries showed such considerable uniformity it was tempting to investigate their mechanism by reproducing them deliberately in the post-mortem room. For this purpose a strong vice was used. It consisted of two parallel steel bars each carrying on a ball-and-socket joint a sliding plate which could be applied to the opposite sides of the skull. The steel bars were joined together, and could be approximated

by two transverse staffs bearing screws. This frame and vice could be applied in the bitemporal, oblique or antero-posterior diameters of the skull. The vice could be applied to the skull either while it was intact or after removal of the calvarium. In our experiments the pattern of fractures involving the base of the skull seemed to be the same whether the calvarium was removed or not.

Bilateral Crush.—With the vice applied to more or less symmetrical points in the temporal areas, the screws were tightened until the bone was heard to crack once or twice. Measurements showed that a transverse line drawn across the plane of the sella turcica in one experiment decreased by 11 mm. when the first crack was heard, and by 24 mm. with the second crack; the antero-posterior diameter being visibly lengthened. The brain appeared to be uninjured and only slightly deformed by this bilateral compression (Fig. 1).

The fractures through the base of the skull could be divided into those occurring regularly and others which were infrequent and inconstant. Three fairly constant main features were observed in the nine cases studied (Fig. 3).

1. In all cases unilateral or more usually bilateral fissures displaced the petrous bone from the great wing of the sphenoid, and from the squamous temporal bone along the petro-squamous fissure. The petrous bone was avulsed from its antero-lateral attachment by a rotatory movement around a vertical axis through the petrous base. The petrous apex travelled the greatest distance, in a backward and inward direction, thus widening the foramen lacerum, and creating a large gap between the petrous and sphenoid (Fig. 2). The carotid canal and artery were thus laid bare. The fracture line usually ran postero-medially to the foramina ovale and spinosum, which were not commonly involved, nor were the acoustic or jugular foramina affected as a rule. In an oblique crush the foramen ovale was involved on one side, the jugular on the other. A small splinter was commonly broken off the tip of the petrous bones.

2. In half the cases the fracture also affected the thinnest part of the petrous temporal bone, that is, the tegmen tympani. In some instances this was neatly separated out as a diamond-shaped plate (Fig. 3, experiments I, IV, V), thus unroofing the tympanic antrum and cavity. Bleeding from the ears was seen in two experiments, and rupture of the tympanic membranes on the one occasion when it was looked for (experiment VI).

3. The fracture commonly extended across the dorsum of the sella turcica, linking up with its fellow which started at the opposite foramen lacerum. With sufficient pressure the base of the skull was actually broken in two, the parts articulating on a transverse hinge. In other words the principal fracture lines were found to run transversely, that is, in the direction of the compression.

Inconstant fractures were a fracture through the superior orbital fissure (experiments III and IX) which appeared before the usual petro-squamous lesion. A small crack of the orbital plate was the first fracture in experiment I. A fracture extending sagittally through one optic foramen and the fronto-ethmoidal fissure appeared in experiment IV. Fractures through the posterior fossa were seen only when excessive pressure had been applied (experiments I and IX); the foramen magnum was then bilaterally narrowed. Occasionally fractures appeared after a delay, while the vice was being kept in place without further tightening.

Antero-posterior Application of Vice.—Here again the effect of compressing the base of the skull was on the whole more one of tearing apart than of squeezing together. As the antero-posterior diameter was shortened and the lateral diameter lengthened, gaps appeared and widened in the cribriform plate, and indeed little else but the anterior fossa was affected. The most important fracture lines ran not perpendicular to, but in the direction of, the compressing force, that is, sagittally, and were apparently due to the anterior fossa being stretched from side to side. Thus the ethmoid sinuses were made to gape by a force that pulled them apart sideways and produced lines running from before backward; and the optic canals were split in the same direction (Fig. 4).

Transverse fractures may appear in the roofs of the orbits, and break off the dorsum sellæ: this may also be associated with chipping a flake off the petrous apex. In general, however, the middle fossa was practically unaffected in antero-posterior compression.

Discussion

Mechanism of Injury to Cranial Nerves

In transverse compression, the maximum distortion of the base of the skull takes place at the foramen lacerum, where, as has been seen, the avulsion of the petrous bone causes the petrous apex to rotate backwards and inwards. This must tend to stretch the sixth nerve as it runs across the increased gap of the foramen, and, together with the chipping off

the petrous apex, affords an explanation for the common involvement of the abducent nerve in lateral crushing injuries. The same mechanism, namely the separation of the anterior part of the petrous bone from the greater wing of the sphenoid, implicates the fifth nerve. The ophthalmic division or the ganglion and roots suffer, either by the splitting and unroofing of the carotid canal, and the destruction of Meckel's cave, or because they are injured by stretching or tearing. It seems that the third and fourth nerve usually escape as they are not running across but medially to the petrous apex (Fig. 5). But they may be caught in fractures through the superior orbital fissure. Pupillary changes may be due to damage to the sympathetic network around the carotid in the foramen lacerum.

The damage to the facial nerve and to hearing is evidently of different origin : it is brought about by the fracture into the tympanic cavity. The deafness is usually of a middle-ear type and most patients recover from it ; in the experiments the internal auditory meatus and probably the labyrinth remain intact. Damage to the middle ear explains both the hæmorrhage from the ear and the penetration of air into the cranial cavity.

In sagittal compression, with its effect on the ethmoidal and optic foramina, the olfactory and optic nerves are specially liable to suffer. In practice this form of crushing is probably much less common than the transverse type. In our clinical material Case 10 seems to have been affected in this way.

Duret (1919) in his classical monograph on head injuries has reached similar conclusions, which were based on experiments similar to ours in method and results, carried out by Hermann (1884), and by Patel near the end of the last century. He stressed in particular the role of the fractured petrous apex in producing the common sixth-nerve palsy (with or without involvement of the fifth), the fractures running parallel to the petrous axis, and his views are similar to our concept of the rotating petrous bone.

X-ray Examination.—In conclusion it should be emphasized that radiography often fails to demonstrate fractures of the base of the skull, especially where routine projections, including Towne's view, are used.

Fig. 6, for example, is the lateral radiograph of an experimentally crushed skull with large gaps between the petrous bones on one hand and the greater sphenoidal wing and the squamous temporal on the other (Fig. 3, experiment V). The crush was such as to produce bleeding from the ears in the cadaver and penetration of air into the basal cisterns, which is well shown on the radiograph. Yet the only radiographic evidence of bone damage is a fine, hardly perceptible fissure rising above the petrous bone.

It is therefore not surprising that in five out of our fifteen patients fractures could not be demonstrated radiographically, although such clinical signs as bleeding from the ears and cranial nerve palsies in nearly all of them left little doubt as to the presence of basal fractures. As in these cases the temporal bone is usually affected, an oblique lateral projection is revealing in most instances ; the tube is directed towards the lateral aspect of the skull at an angle of 35° from the vertical, with the central ray pointing towards the feet (Fig. 7).

Summary

1. The records of fifteen cases of crushing injury to the skull are given.

2. This type of injury, when the patient survives, usually leads to no loss of consciousness, even though there is a fracture of the base of the skull and injury to cranial nerves. The absence of *acceleration concussion* presumably explains the preservation of consciousness.

3. Crushing injuries were applied to the cadaver, and the pattern of basal fractures was fairly constant in most experiments ; their bearing on the clinical picture is discussed.

4. The difficulty in demonstrating fractures of the base of the skull by radiograph was confirmed in these experiments.

We are particularly indebted to Dr. E. S. Schuster, O.B.E., who devised and constructed the vice used for the experimental studies, and to Dr. A. H. T. Robb-Smith and his staff for providing facilities in the post-mortem room.

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PLATYBASIA: WITH CASE REPORT

BY

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From both pathological-anatomical and clinical aspects the condition called *impressio basilaris cranii*, " basilar impression," or " basilar invagination," was well known in the last century. In the last fifteen years it is referred to more often as " platybasia," in which the " basal angle " (the angle between the lines through the sphenoidal planum and clivus) is increased beyond the normal 135–140°.

Rokitansky (1846) is usually recorded as having first described it without any special name, but Berg and Retzius (1855) described it under the name *impressio baseos crani*. The first clinical observation dates from Boogaard (1865). Later it was described by Virchow (1857), Grawitz (1880), Schiffner (1878), Homén (1901), Krause (1911), and others. From the radiological point of view, Schüller (1911) had called attention to the condition. As Chamberlain (1939) had described four cases of platybasia, two of which had been successfully operated on by Temple Fay, it attracted attention in America. The term " platybasia," originally Virchow's, was introduced into the English-speaking literature by Chamberlain. Five cases were reported by Gustafson and Oldberg (1940), with a review of the whole subject. They found a connexion between the malformations around the foramen magnum and platybasia, and postulated that craniovertebral malformations have some relation to the hydrodilatation of the central nervous system (hydrocephalus, hydromyelia). Seven neurological cases with several malformations of the occipital bone, atlas, and axis were described by List (1941). His report discusses thoroughly the pathogenesis with regard to the ontogenetic factors, the mechanism producing the clinical picture, the diagnosis, and the treatment. Blomquist (1944) gives a detailed review of the whole question of the " basialis impressio," and data from the literature with reference to a case of his own, diagnosed post mortem. The only shortcoming in his paper is that he does not even mention the possibility of surgical treatment, although it had come rather to the fore in the literature of the past fifteen years.

Primary Basilar Impression.—According to present-day opinion, basilar impression may be primary or secondary. Primary basilar impression is the result of a defect in craniovertebral development arising, according to Virchow's and Grawitz's suggestions, from the early ossification of the spheno-occipital suture, a defect in chondrogenesis and ossification. The posterior fossa fails to keep up in developmental pace with the vertebræ; the atlas overgrows the foramen magnum and does not join the condyles but fuses with the undermost part of the clivus and with the posterior rim of the foramen magnum. Schiffner suggested that the skull weighs heavily upon the atlas during intrauterine life, so that the atlas fuses with the occipital bone and penetrates into the cranium. Becker pointed out in a thorough work that the basilar impression and the fusion of the atlas were to be considered as malformations and neither as variants of development nor as a caudal-progressive transformation leading to a future form of mankind, as suggested by others to account for the fusion of the atlas. He emphasizes that the fusion of the atlas and the basilar impression are in co-ordination and not in subordination, as they do not depend on each other in any genetic sense; both are determined in the third or fourth embryonal week. The primary idiopathic basilar impression is to be considered as a disorder of development, a view well supported by cases of basilar impression with other associated defects of development, such as, for example, spina bifida (List, 1941). Peyton and Peterson (1942) emphasize that the cases of basilar impression considered as defects of development are always accompanied by fusion to a varying degree of the atlas and occipital bone.

Secondary Basilar Impression.—This may occur in any diseases causing softening of the bones (Paget's disease, rickets, osteomalacia, hyperparathyroidism, lipoidosis, caries, senile osteoporosis, osteitis deformans, etc.). Owing to the plasticity of the basis, the uppermost cervical vertebræ—

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heavily pressed upon by the skull—are forced into the foramen magnum and the posterior fossa (Brailsford, 1944). Such cases of secondary platybasia are recorded by Schüller (1911), von Recklinghausen (1897), Homén (1901), Stilling (1890), Catola (quoted by Tscheslog), Kecht (1932), Tscheslog (1940), Antoni (quoted by Tscheslog), and Wycis (1944). The atlanto-occipital fusion is not a necessary concomitant of the secondary basilar impression.

Clinical and other Features

Skeletal Signs.—In the symptomatology there are some skeletal signs which provoke no particular complaints, such as the striking short neck, a certain restriction in movement of the head, the low hairline at the back of the neck. These signs may increase in time, but not necessarily. The head may sink between the shoulders and become almost fixed. The basilar impression may assume clinical importance by causing neurological signs of direct compression on the pons and medulla oblongata, as in Bézi's case (1931) where the direct compression by the odontoid process caused softening in the medulla oblongata ; or by the herniation of the cerebellar tonsils ; or by hydrocephalus and hydromyelia due to disturbances of the intracranial hydrodynamics, and occasionally by simultaneous defect of development of the central nervous system (for example, syringomyelia). From the point of view of symptomatology the cases of marked basilar impression of Stenvers (1916) and of Merio and Risak (1934), which were dominated by endocrine disturbances, are of some interest. In Stenvers' case of adiposogenital dystrophy there was found at post-mortem examination a macroscopically and microscopically normal pituitary body, but the third ventricle and the infundibulum had been dilated so enormously by the hydrocephalus that there was almost no basal wall of the ventricle, so that the author considered the clinical picture to be the result of the destruction of the autonomic centres. In one of their cases Merio and Risak considered eunuchoidism to be the effect of a lesion of the pituitary body due indirectly to basilar impression or to the internal hydrocephalus resulting from the basilar impression. In two other cases of theirs myxœdema was ascribed to disturbances of the circulation in the thyroid gland due to the very markedly lordotic cervical spine.

Neurological Signs.—The neurological signs (which may never be evident in cases of primary basilar impression during the whole life) develop gradually as a rule (Baruch, 1932 ; Tscheslog, 1940 ; Gustafson and Oldberg, 1940 ; Walsh and others, 1941 ; Wycis, 1944 ; etc.), although there are cases recorded with signs of rapid onset (Becker, 1940 ; Bodechtel and Guizetti, 1933). The symptoms may vary ; the most striking of them are paraparesis, eventually quadriparesis, ataxia, nystagmus, disturbances of swallowing, difficulties of articulation, dyspnœa. In cases of secondary basilar impression the primary disease (for example, Paget's disease) may present many additional symptoms.

Radiology.—The *x*-ray investigation of the skull establishes the diagnosis. On the *x*-ray films in the lateral view the basal angle is increased to more than the normal 140° (though some authors allow 150° as the normal), the clivus approaches the horizontal line in different degrees ; the shadows of the atlas and the odontoid process are above the so-called Chamberlain's line (the line between the posterior rim of the foramen magnum and the posterior edge of the hard palate), though normally they are below it. The foramen magnum is usually pressed upwards into the posterior fossa, and is narrowed, eccentric, and abnormal in shape. In cases of congenital origin the posterior arch of the atlas is usually fused with the lower edge of the occipital bone, and the odontoid process may reach over the foramen magnum. The spinous processes of the upper cervical vertebræ may be fused with each other. Encephalography usually shows a varying degree of dilatation of the ventricles.

Differential Diagnosis.—In the differential diagnosis cervical syringomyelia (Gustafson and Oldberg), chronic hydrocephalus (*ibid*), cerebellar tumour (Bodechtel and Guizetti), bulbar encephalitis (*ibid*), angle tumour (Adam-Falkiewiczowa and Nowicki, 1931), etc., must be considered. Gustafson and Oldberg suggest that in each case of cervical syringomyelia and in some cases of chronic hydrocephalus careful *x*-ray examination of the upper cervical spine, the foramen magnum, and the base of the skull should be undertaken.

Treatment

Treatment may be exclusively surgical : this, however, has been practised only in the last fifteen years. The patient whose case is recorded by Juhlin-Dannfelt (1933) died some weeks after operation. One of the four cases reported by Ebenius (1934) died while being operated on ; three of them had slightly improved after surgical treatment. Two of the four cases recorded by Chamberlain (1939) had been operated on successfully by Temple Fay. In the same year at the International Congress of Neurologists in Copenhagen surgical treatment was suggested by Oljenick :

he advised freeing the cerebellar tonsils which had been forced into the cervical canal from adhesions, and by this means bringing them back into the skull. In 1940 Gustafson and Oldberg described five patients who were operated on; two of them died. Dereymaeker (1941) described one patient who was slightly improved after surgical treatment. Of the six surgically-treated patients recorded by List (1941), three died of respiratory paralysis. The first of List's patients had been operated on in 1935 by Kahn. The cases recorded by Walsh, Camp, and Craig had been successfully operated on by the latter in 1941. Recently (1944) Wycis operated with excellent results on a case of basilar impression due to Paget's disease.

The surgical treatment consists essentially of upper cervical laminectomy with suboccipital decompression. List and Wycis suggested that the dura be left open, but Craig also had a good result with closure of the dura.

The following case is considered to be worth recording because the patient, who had severe symptoms, became practically free from complaints after operation and there are only a few instances reported of cases which have been operated on successfully.

Report of a Case

A farmer, aged 17, was admitted to hospital on Sept. 5, 1946, having been referred by his parents.

History.—Increasingly for one and a half years he had had headaches of the vertex, dull in character and most marked in the morning. He had also experienced occasional dizziness, staggering when working, and several attacks of nausea. For over a year swallowing had become difficult, and at the time of his admission he could not swallow fluid because it regurgitated through the nose. In the eight months before admission his speech had become gradually nasal and mumbling. Over the same period his left upper limb, then the left lower, later the right upper, then the right lower limbs had become clumsy and weak. He had been unable to walk for seven months and had been lying on his back or on his abdomen; he could not sit up by himself, and if he had been lifted up he had dizziness and dyspnœa. One month before admission the left side of his face became congested, but this settled down again. Since that time the sight of his left eye had been poor. He suffered from constipation and incomplete emptying of the bladder. His condition had not changed in the last four months. His parents had not taken him to the clinic because their doctor told them it was not worth while, that he would die anyway.

Family and past histories were irrelevant.

Examination.—He was an asthenic short boy rather undeveloped for his age. The skull was normal in size and form, and was painful to percussion. The neck was short and markedly limited in all movements. There was on the ribs the so-called " rosary " of rachitic origin. There was marked lumbar lordosis, and marked dyspnœa on sitting up. The pulse rate was 76 per minute, the blood pressure 150/75 mm. Hg. The senses of smell and sight were good, and visual fields and fundi were normal. The pupils were medium-sized and circular; they reacted well to light and accommodation. The left pupil and palpebral fissure were smaller than the right. External ocular movements were full. There was a coarse, irregular, horizontal nystagmus when the patient looked to the right, and a finer one when he looked to the left. The trigeminal points were painful to pressure. There was bilateral constant wrinkling of the forehead which could be voluntarily abolished. The soft palate showed definite paresis on the left side with absence of the palatal reflexes on both sides. When he swallowed, the fluid came back through his nose. Speech was nasal. The tongue deviated to the left. His movements were slow; there was a spastic quadriparesis;

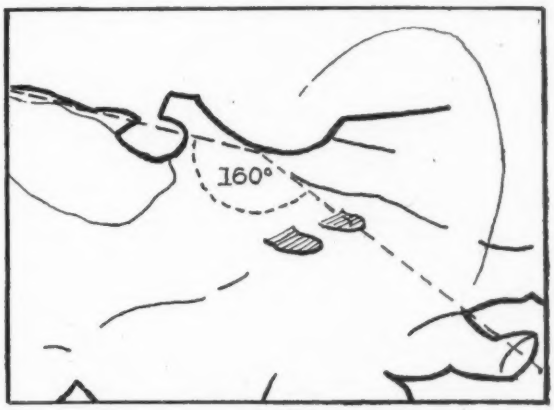

FIG. 1.—Diagram showing the increased basal angle.

he could not sit up, stand up, or walk, but there remained some motor powers in the extremities. The upper limbs were in the position of flexion, both lower limbs in extension. The fingers were in slight flexion, especially on the left hand; their movements were clumsy, weak, and limited. There was very marked atrophy in the muscles of both upper limbs, especially in the shoulder, thenar, hypothenar, and interossei muscles. Fasciculations sometimes occurred, particularly on the left side of the body. There was static and kinetic ataxia in the upper and lower extremities. The deep reflexes were markedly exaggerated, with knee and ankle clonus on both sides. On both sides plantar reflexes were extensor and abdominal reflexes and Meyer's and Léri's signs very sluggish. There was no sensory disturbance, but partial bladder and total bowel retention.

We could not obtain any cerebrospinal fluid by lumbar puncture. By cisternal puncture only one or two drops were obtained, even with suction.

A provisional diagnosis was made of syringomyelia in the upper cervical region.

X-ray examination clarified the diagnosis. The basal angle was increased to 160° (Fig 1). The arch of the

atlas was well delineated ; it was not fused with the occipital bone, but they were nearer than usual to each other. The foramen magnum was asymmetric, flattened in the antero-posterior dimension, and narrowed. The upper cervical spine was markedly lordotic. Ventriculography was performed to complete the examination. There was moderate asymmetric hydrocephalus.

Operation.—On Oct. 17, 1946, the patient was operated on by Prof. Dr. K. Sántha. The patient having been placed in the face-down " cerebellar " position, under local anæsthesia, the surroundings of the foramen magnum and the posterior arches of the atlas and axis were exposed through a mid-line incision extending from the external occipital protuberance to the seventh

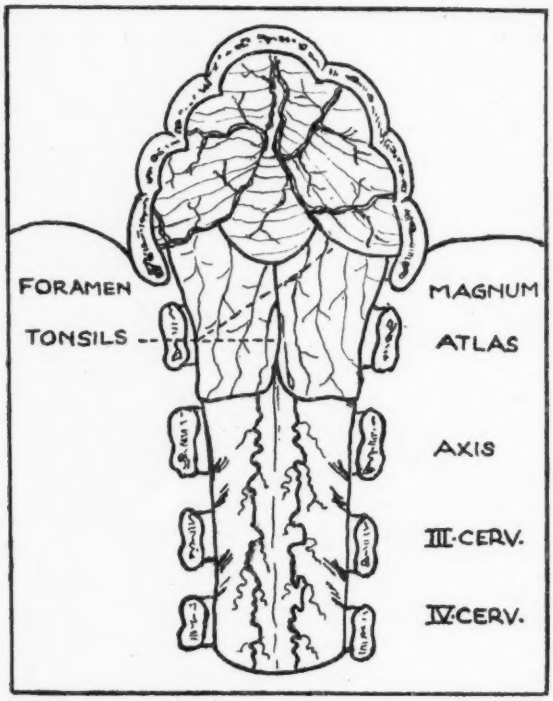

FIG. 2.—Diagram showing the situation at operation

cervical vertebra. The spinous processes of the third and fourth vertebræ were exposed only to get better access to the arch of the axis. The lower part of the occiput showed a flat indentation in the mid-line. The posterior arch of the atlas was large but smooth ; there was no spinous process on it. The spinous process of the axis was large and bifid on the end ; the arch was wide. The spinous processes of the third and fourth vertebræ were normal. The distance between the atlas and axis was normal but the atlas and occipital bones were nearer to each other than usual, although they were not fused.

The posterior arches of the axis and atlas were removed and then from a burr hole on the right side of the occipital bone the rim of the foramen magnum was removed as well. The posterior rim of the foramen magnum was seen to extend far forwards below the cerebellar hemispheres so as to compress the dura with the effect of nipping the underlying tonsils. In the mid-line a huge bony comb was seen between the two cerebellar hemispheres, so that in order to progress we had to make a burr hole on the other side also and from there remove the posterior rim of the foramen magnum on the left side. At the end the thick part in the mid-line was pinched off with rongeur. The median bony comb was seen to extend far upwards and to rise inwards for over a half inch. The bone surrounding the foramen magnum was removed in a semicircle about one and a half inches high, and the comb rather more than this inwards. After opening the dura the arachnoid was seen to be normal, and a large amount of cerebrospinal fluid was obtained by opening it. The two cerebellar tonsils surrounded the bulbospinal border as flat structures and extended into the spinal canal to the level of the axis. The lower pole of the inferior vermis reached to the rim of the foramen magnum (Fig. 2). The tonsils, which were fixed only by some arachnoidal filaments, were freed and their poles lifted ; only then was it possible to see the inferior cerebellar arteries, which had slipped down. We easily separated the tonsils from each other. The dura was left open as a decompression ; the muscles and ligaments were closed with interrupted catgut sutures and the skin with interrupted black silk sutures. At the very beginning of the operation the patient had suffered respiratory paralysis, but this recovered and during the operation his condition was good.

Postoperative Period.—The neurological signs improved gradually, so that at his discharge five weeks after operation he was walking without any help, though the gait was still unsteady. There was slight ataxia in the finger-to-nose and heel-to-knee tests, and coarse nystagmus on looking to either side. No other signs, not even the marked lumbar lordosis, were seen.

Five months after operation he came alone by train to a follow-up examination. He stated that he had been working at home as a farmer. His one complaint was that he was not quite steady, particularly when walking in the dark. There was slow, coarse nystagmus on both sides. Gait was slightly ataxic but he was able to walk even with closed eyes. There were no other pathological signs. Of the former marked atrophy in the hand muscles there was nothing to be seen, and the muscles were well developed. He was able to turn his head to either side quite quickly and well, to bend forward on his chest ; bending backwards was rather painful.

Comment

This case is considered to be a secondary platybasia of rachitic origin. At operation there were no signs of any developmental malformations of the atlas or of the cervical vertebræ ; this supports the diagnosis. The rapid improvement of the neurological signs after operation confirms that there may be no malformations of the central nervous system such as syringomyelia. The (bulbospinal) neuro-

logical signs are perfectly explained by the findings at operation.

We should like to call attention to the fact that in some of the cases of primary platybasia there is only a limited degree of recovery achieved by decompression—a fact which is supported by some reports in the literature. Presumably in these cases we are faced with developmental malformations not only of the skeleton but of the central nervous system as well, and in these cases the simple decompression does not solve the problem. In the cases of obviously primary platybasia it is to be recommended that the exposed part of the spinal cord be examined very carefully at operation, and if there is a syringomyelia probably Puusepp's operation may be carried out at the same time as the decompression. Most of the cases in the literature with no satisfactory improvement after surgical treatment appear from the descriptions to be primary, and indeed in none of these cases is there record of any skeletal diseases as an ætiological factor.

Our similar case is a woman of 24 who, some months before the former case, was admitted to hospital with severe ataxia, four years' progressive quadriparesis, astereognosis in both hands, and hypoæsthesia below the third cervical dermatome. High cervical laminectomy and suboccipital decompression (Prof. Sántha) produced only slight improvement in the neurological signs. She had complete occipitalization (fusion) of the atlas. We could not find any signs indicating a secondary origin of the platybasia, so it was considered to be a developmental malformation. At operation the cervical spine did not show any signs of syringomyelia; it is possible, however, that this patient did not recover sufficiently because she had some additional developmental malformation of the central nervous system.

As surgical treatment is the only possible therapy, it should be advised in every case, even in the cases of undoubtedly primary origin. We may hope for complete recovery of the neurological signs, not only in secondary but in primary cases (Walsh and others, 1941).

Summary

1. The literature regarding platybasia is reviewed.

2. A case of secondary platybasia of rachitic origin is described which was relieved by upper cervical laminectomy and suboccipital decompression.

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VIRUS DISEASES OF THE CENTRAL NERVOUS SYSTEM: A REVIEW

BY

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CLASSIFICATION

The virus diseases of the central nervous system are of growing importance. Some are apparently increasing in incidence, others are newly recognized. Even in a country like Great Britain the more exotic types may be seen in these days when air travel has brought the remotest parts of the tropics within one or two days' travelling time of North-western Europe. They may be classified into two main groups (Rhodes, 1948):

A. Primary neurotropic virus infections with recognized clinical syndromes, whose characteristic signs and symptoms result from involvement of the central nervous system.

B. Secondary infections due to ordinarily non-neurotropic viruses, in which involvement of the central nervous system occurs as a complication of a primary infection elsewhere in the body.

A. Primary Neurotropic Virus Infections

The primary neurotropic virus infections may be differentiated on the serological reactions of the viruses, of which about forty antigenic types are known. A more useful classification is based on the anatomical incidence of the pathological lesions, with subdivisions, some based on the antigenic structure of the causative viruses, thus:

Virus meningitis and meningo-encephalitis

Lymphocytic choriomeningitis
Pseudolymphocytic choriomeningitis
Meningo-encephalitis due to the virus of mumps
Durand's disease

Virus encephalitis

1. Arthropod-borne encephalitides

i. *Mosquito-borne*

(*a*) St. Louis encephalitis, Japanese B encephalitis, and West Nile infection

(*b*) Equine encephalomyelitis

Borna disease, Russian equine encephalitis

North American equine encephalitis (Eastern type), North American equine encephalitis (Western type), Venezuelan equine encephalitis

Semliki Forest virus and Bunyamwera virus infections

ii. *Tick-borne* (*Ixodes sp.*)

Louping ill

Russian spring summer encephalitis (Far Eastern variety), and Russian spring summer encephalitis (Western variety)

iii. *Vector unknown*

Australian X disease

2. Rabies

Ordinary street virus spread by canines
'Oulou fato' virus spread by canines
Trinidad rabies spread by the vampire bat—(*Desmodus rotundus murinus*)

3. Encephalitis lethargica (Von Economo's disease), Japanese A

Ascending myelitis due to B virus

4. Encephalitis possibly due to viruses as yet unidentified

Virus poliomyelitis

Non-Lansing type
Lansing type

Miscellaneous viruses possibly causing paralysis simulating poliomyelitis

MM virus
Encephalomyocarditis virus
Mengo virus

B. Secondary Virus Infections of the Central Nervous System

1. Post-infective encephalitis

Rarely follows dengue, herpes febrilis, herpes zoster, infective hepatitis, influenza, lymphogranuloma inguinale, measles, mumps, rubella, sandfly fever, variola, and varicella.

2. Post-vaccinal encephalitis

Occasionally follows vaccination with living virus vaccines against smallpox (vaccinia) and against yellow fever.

Vaccination against rabies is occasionally complicated by neurological accidents. This condition is probably not the result of virus action, but it merits discussion in this section.

PRIMARY VIRUS INFECTIONS

Virus Meningitis and Meningo-encephalitis

The best known of this group is lymphocytic choriomeningitis. The virus was first isolated by Armstrong and Lillie in 1934. The disease has a world-wide distribution. Infection is usually contracted from house mice, the normal carriers of the virus. Experimentally, the virus can be transmitted by arthropods, but the common route of infection is probably via the respiratory tract by the inhalation of infected particles, or by ingestion of food contaminated by infected rodent excreta.

Armstrong (1941) recognizes three forms of this disease, namely influenzal, meningitic, and meningo-encephalitic types. He notes that most infections have no symptoms of meningeal involvement.

In typical cases the onset of the illness is sudden, with coryza and fever, followed by signs and symptoms of meningitis, headache, photophobia, vomiting, stiffness of neck and back, and positive Kernig's sign, often associated with squint, nystagmus, and papillœdema. The febrile illness lasts three to six weeks and is rarely fatal. MacCallum and Findlay (1939) have described one case with paralysis of the lower limbs closely simulating poliomyelitis.

The cerebrospinal fluid, usually clear, is under increased pressure. The globulin content is increased, but sugar and chloride are normal. The cell count shows an increase in lymphocytes, usually to 100 to 250 per c.mm., but occasionally up to 1,500 per c.mm.

Pseudolymphocytic choriomeningitis is a similar condition caused by a similar, but antigenically distinct virus (MacCallum and others, 1939).

Discussing an outbreak of virus encephalomyelitis, Jennings (1947) suggests that other as yet unidentified viruses may also be concerned in causing lymphocytic meningitis. Tidy (1946) has noted the close similarity between benign lymphocytic meningitis and nervous forms of glandular fever.

Mumps virus may cause primary meningo-encephalitis. Indeed such cases are not uncommon.

Durand's disease (Findlay, 1942) is caused by a virus transmissible to guinea-pigs. Two laboratory infections in human beings have been described in North Africa. The illness in one of them was characterized by a biphasic temperature chart. During the second bout of fever the patient had intense headache, nausea, and vomiting, with occasional neuralgic pains in the back of the neck, thorax, and calf.

It is not known whether this virus naturally infects Man and, if so, whether the infection is widespread. Although this condition is here grouped with the virus meningitis, this is a tentative classification. It has been shown that there is no immunological relationship with the virus of choriomeningitis.

Virus Encephalitis

1. Arthropod-borne Encephalitis

Many of the virus infections of the central nervous system can be grouped together as arthropod-borne virus encephalitides since the viruses have been isolated from mosquitos, mites, and ticks, and there is convincing evidence that these invertebrate hosts are vectors and, occasionally, reservoirs of infection (Hammon, 1948). All are primarily infections of birds or animals. Man is infected only accidentally. Most of these infections have a limited geographical distribution but, as a group, they occur over wide areas of the world. They have a clearly defined seasonal incidence, depending on the seasonal prevalence of the arthropod vector. The group can be divided according to the common vector to Man into a mosquito-borne group and a tick-borne group.

Mosquito-borne Encephalitis.—The mosquito-borne infections can be subdivided on the antigenic relationship of the viruses into two further groups, namely St. Louis encephalitis group and the equine encephalomyelitis group.

St. Louis Encephalitis Group.—St. Louis encephalitis derives its name from an epidemic which occurred in St. Louis in 1933. Another outbreak occurred there in 1937. Since then outbreaks have occurred in other areas, and it is now clear, from serological studies, that this disease has a wide distribution in the United States. The virus infects domestic and wild birds. It is spread amongst them by mosquitos, such as *Culex tarsalis*, and the chicken mite *Dermanyssus gallinæ*. The latter acts as a true reservoir host, for infection may persist in them for several months and may be hereditarily transmitted to succeeding generations. The virus appears to be transmitted to Man by mosquitos, especially *Culex tarsalis*. As is to be expected, opportunities for infection of Man are greatest in rural and suburban areas.

An epidemiologically and clinically similar type of encephalitis, known as Japanese B encephalitis, has been recognized in Japan for many years. This also is a summer disease and large outbreaks involving thousands of cases have occurred. It is also spread by mosquitos, probably *Culex tritæniorhynchus* and *Culex pipiens* var. *pallens*. Serological studies have shown that there is antigenic overlap but not identity with the virus of St. Louis encephalitis. Sabin (1947) has recently noted the occurrence of cases of Japanese B encephalitis on Okinawa and the neighbouring islands.

The West Nile virus was isolated from the blood of an African woman in the West Nile Province of Uganda, East Africa, who had fever but no definite signs of an encephalitis. She subsequently developed antibodies in her serum against the virus, so there is little doubt that her infection was actually due to the virus. The virus particles were approximately the same size as those of the virus of St. Louis encephalitis. By a series of cross-neutralization tests, Smithburn (1942) found that the West Nile virus was immunologically related to but distinct from the viruses of St. Louis and Japanese B encephalitis. Anti-serum against the West Nile virus does not neutralize either of these viruses. Vaccination with either of the three viruses causes enhanced resistance to the homologous strain only. The immunological relationship is shown by the fact that anti-sera against the St. Louis virus may cross-neutralize the West Nile virus and anti-sera against Japanese B virus have some power to cross-neutralize both the West Nile and the St. Louis viruses.

It is noteworthy that these antigenically related viruses were isolated from widely separated regions of the world—St. Louis in North America, Japanese B in Japan, and the West Nile in Central Africa.

Equine Encephalomyelitis Group.—Equally widespread are the viruses constituting the equine encephalomyelitis group. These infections are also mosquito-borne. The virus of the Western type of North American equine encephalitis has also been isolated from chicken mites and from wild bird mites *Liponyssus sylviarum*, and possibly *Dermanyssus americanus* (Hammon, 1948). Of this group, European Borna disease of horses and Russian equine encephalitis are not known to infect Man. Antigenically these two viruses are distinct from each other and from the Eastern and Western types of North American equine encephalitis, which in turn are distinct from each other, though they share common antigens. Similar or related viruses have been described from Brazil (related to the Eastern type) and from the Argentine (related to the Western type). The Venezuelan type is distinct from both the Eastern and Western types.

The Semliki forest virus, and the Bunyamwera viruses were isolated from batches of mosquitos (Smithburn, 1948). In their physical and immunological properties, these viruses are related to the equine encephalomyelitis group. That they can cause infections of Man is apparent from the finding of neutralizing antibodies in sera from individuals in this region. However, the clinical characteristics of the illness they cause is not known. It is also not known whether they ever cause symptoms of encephalitis.

Human cases of encephalitis, due to the viruses of equine encephalomyelitis, have been described from many parts of North America. As is to be expected the disease most commonly affects those living in rural areas where wild and domestic birds are the source of infection. Man and horses are accidental hosts and the infection is transmitted to them by mosquitos, especially *Culex tarsalis*.

Recently Hammon (1948) has suggested that this whole group of arthropod-borne encephalitides may be inter-related and derived from a common stem virus. The clinical manifestations are similar. Following an incubation period of from four to twenty-one days, the onset of illness is acute, with severe headache, dizziness, photophobia, nausea and vomiting, and fever usually lasting one to two weeks. Some cases do not develop definite signs of involvement of the central nervous system, but in typical cases these symptoms at the onset of illness are followed by encephalitic symptoms, neck rigidity, and mental confusion ; then nerve paralysis, especially affecting the muscles of the eyes, causing squints and diplopia, may develop. Aphasia may occur. Often the patient becomes stuporose or even comatose. Death occurs in approximately one-third of the cases, nearly always within a fortnight of the onset. Of the non-fatal cases, two-thirds recover completely. The remainder are left with sequelæ, such as headaches, irritability, loss of memory, and lethargy.

During the acute phase, the cerebrospinal fluid is clear but under increased pressure. There are from 50 to 250 cells per c.mm., including up to 50 per cent. neutrophils in the early stages. Later monocytes predominate.

In the cases of Japanese B encephalitis occurring amongst American military personnel on Okinawa, Sabin (1947) noted that the outstanding clinical features were " lethargic " consisting of drowsiness, lethargy, mental confusion and disorientation, and semicoma, or complete coma in the more severe cases occurring in association with high fever, nuchal and spinal rigidity, leucocytosis, and pleocytosis.

Tick-borne Encephalitis.—Louping ill, a well known disease of lambs in Scotland and North England, is so called because of the peculiar gait of affected lambs. It is transmitted by ticks, *Ixodes ricinus*, which in their larval stage become infected by sucking blood of an infected sheep, and are then infective in their nymphal and adult stages.

Laboratory infections of Man have occurred, four in the United States (Rivers and Schwentker,

1934), and two in Europe (Wiebel, 1937 ; Wesemeier, 1938). More recently in North England two naturally acquired infections in Man were described following bites of these ticks (Davison and Neubauer, 1948). The illness resembled that seen in three of the six laboratory infections in having a biphasic character, the meningo-encephalitic phase following the influenzal-like phase after several days of comparatively good health. A few days after the patient's exposure to tick bites, the illness began with malaise, headache, and fever, which continued for a week. There was then an afebrile interval of one to two weeks during which the patient recovered. Then the symptoms returned with increased intensity : severe headache with fever, vomiting, bradycardia, drowsiness, insomnia, confusion, tremors, and ataxia. The physical signs included neck stiffness, papillœdema, and cranial nerve palsies. The blood showed a leucocytosis of 10,000 to 12,000 per c.mm. with 70 to 80 per cent. neutrophils. The cerebrospinal fluid, which was clear or slightly blood-stained, contained from 50 to 500 cells, mostly lymphocytes, per c.mm. The protein content was slightly raised. The fever abated in a few days and the symptoms had largely cleared in a week, but it was a few weeks before one of the patients fully recovered. The other patient has permanent sequelæ. In convalescence the sera of these patients neutralized the virus of louping ill.

Russian spring summer encephalitis is also spread by a tick, *Ixodes persulcatus*, and probably also other species. Two varieties are recognized—a Far Eastern type, which gives rise to a severe, often fatal, disease in Man, and a milder Western type. The viruses are very closely related to that of louping ill. The Eastern type may be identical with it.

A disease known as Australian X disease, having resemblances to louping ill, occurred in Australia. It was first recognized in 1917 and 1918. These cases were characterized by an incubation period of from five to twelve days, a sudden onset of vomiting, headache, fever, drowsiness, twitchings, and muscular weakness and inco-ordination, and in children convulsions. The death rate was 70 per cent., death usually occurring within the first week. Those cases that recovered had fever for ten or twelve days, after which they rapidly improved and recovered without permanent sequelæ.

The cerebrospinal fluid showed pleocytosis. A virus was isolated from several cases. This virus was studied for its effect on experimental animals. In Man it was noted that there was a widespread destruction of Purkinje cells similar to that seen in monkeys infected with louping ill. As this virus has not been maintained, its relationship with louping ill and with the other viruses causing encephalomyelitis in Man has not been determined. It seems, however, to fall into this group of diseases.

The Diagnosis of Virus Encephalitides.—On clinical findings it is usually impossible to name the causative virus of a case of encephalitis. Fortunately reliable laboratory tests are available by which it may be identified. The first of these is the isolation of the virus from the blood or cerebrospinal fluid by the inoculation of experimental animals, usually the mouse, intracerebrally. Once isolated, the virus can be definitely identified in the laboratory by a detailed study of its antigenic and other characteristics. However, in many cases it is not possible during the life of the patient to isolate the virus, either from the blood or cerebrospinal fluid. In such cases the identification may be achieved by immunological methods. The most commonly used is the neutralization test. Known viruses are tested against the patient's serum. To be significant, it must be shown that, from being negative before or at the onset, or shortly afterwards, this test becomes positive later, usually after the first week of illness, or in the patient's convalescence. Complement fixation tests have also been evolved of value in the laboratory diagnosis of these virus infections. Antigens prepared by a benzene extraction method have given results superior to those given by antigens prepared by other methods (Espana and Hammon, 1947).

Prophylactic Vaccination.—In passing, it is of interest to note that formalinized vaccines prepared from infected mouse brains, or from chick embryos, have been found to be effective in conferring immunity against several of the virus encephalitides. These vaccines have been used to immunize large numbers of American soldiers in the Far East without serious untoward effects (Sabin, 1947).

2. Rabies Group

Rabies is an acute infection of the central nervous system caused by a virus, transmitted to Man by the bite of a rabid animal or by the contamination of abrasions or cuts by saliva of a rabid animal. There are two epidemiological types, namely the natural disease as it occurs in wild animals, and the urban type which is maintained in domestic dogs. In different parts of the world different animals are mainly responsible for the infection of Man. In Western Europe it is usually a dog. In Eastern and South Eastern Europe rabid wolves may also attack Man. In North Africa it is also the dog. In Central Africa the disease is often transmitted by jackals, occasionally by hyænas. In South Africa the important vector is the yellow mongoose, or meerkat, and occasionally other

small wild carnivora. In the United States coyotes as well as dogs may be concerned. In Trinidad the disease is transmitted by the vampire bat, *Desmodus rotundus*.

A number of different strains of rabies virus exist. Recently isolated strains from dogs are called street virus. Most street virus can be transformed, by passaging in series through rabbits inoculated intracerebrally, into *virus fixe* or fixed virus. *Reinforce* strains have an unusually high virulence for laboratory animals, possibly also for Man. The virus introduced into the wound invades the nerves and migrates to the brain, producing an acute fatal encephalitis. The incubation period is very variable—from ten days to over three years, commonly about three to twelve weeks. The first symptom is usually irritation at the site of the infecting bite. This is followed by a period of excitement characterized by constant activity, irritability, apprehension, and insomnia. There is increased reflex activity, typically manifesting itself in the classical hydrophobic symptom of painful spasmodic contractions of the throat when attempting to swallow. As the disease progresses, the paroxysms become more frequent and there may be generalized convulsive seizures. Later paralysis supervenes, and when the respiratory centres are involved, death occurs. The disease runs a rapid course and always ends fatally, usually within five days of the onset of symptoms. In some cases paralytic symptoms dominate the picture.

The Trinidad virus, spread by vampire bats, *Desmodus rotundus*, causes rabies of cattle (*mal de caderas*). In Man, it causes an ascending Landry-like type of paralysis.

Rabies, unless suspected, may be mistakenly diagnosed in the beginning as hysteria. The diagnosis is confirmed by the inoculation of laboratory animals, usually the rabbit or mouse, intracerebrally with suspensions prepared from the brains of suspected cases. These subinoculated animals develop the paralytic form and the characteristic Negri bodies can be demonstrated in sections of the brain.

Prophylactic vaccination with suspensions of rabbit spinal cord of patients bitten by a suspected rabid animal is occasionally followed by signs of serious damage to the central nervous system. These neuroparalytic accidents may take the form of a Landry-type of ascending paralysis with a death rate of about 30 per cent., or of dorsolumbar cord involvement with a death rate of about 5 per cent. More rarely cranial nerves are affected. The ætiology of these neuroparalytic accidents is discussed later in this paper. To avoid this complication, efforts are being made to develop a more highly refined vaccine in which the virus is inactivated by ultra-violet light.

The urban type of rabies may be controlled by the measures in vogue for the last hundred years to prevent any dog from biting another for a period of the longest latency of the disease. These are destroying all ownerless dogs, quarantining all owned dogs while rabies prevails, and for at least six months after the last reported case, and quarantining all imported dogs for six months. Vaccination of dogs, using killed virus vaccine, is recommended for use in places where protracted quarantine cannot be enforced, or where the disease is present in wild animals. If vectors among wild animals are drastically reduced by hunting and trapping, the disease cannot persist (Johnson, 1948).

The virus of pseudorabies or mad itch, primarily a disease of animals, has no relation to the virus of rabies.

3. Encephalitis Lethargica

Sleepy sickness has occurred in previous centuries, but the modern interest dates from the first world war, when a widespread outbreak occurred in Western Europe. In England, the first cases were recorded in 1918. In 1924 over 5,000 cases were notified. The number of cases has progressively fallen since then.

These cases were characterized by an incubation period of three to twenty-one days, usually ten to fourteen days. At the onset the patient complained of lethargy, insomnia, headache, giddiness, vomiting, sweating, and fever. The illness then assumed one of several types. In the mesencephalic type there was somnolence, apathy and lethargy, and stupor. In the focal type variable affections of the cranial nerves were seen, giving rise to various oculomotor dysfunctions, including ptosis, strabismus, diplopia, and bilateral ocular muscular paralyses, and occasionally to aphonia. The face was characteristically impassive. In some countries epidemics of hiccough occurred co-incidentally with encephalitis, and these may have been another manifestation of this disease.

The illness lasted from four to ten weeks. About 50 per cent. of the patients died. Many of those that recovered have permanent sequelæ, including mental disorders, Parkinsonism, and other manifestations of damage to the mesencephalon. In children a change to an amoral disposition sometimes occurred.

The virus responsible for encephalitis lethargica remains unknown. As the first outbreaks coincided with the pandemic of influenza, it has been suspected that there was an association between the two conditions, but there is little evidence of a

direct relationship. The virus of *Herpes febrilis* was isolated from the brains of several fatal cases, and from the nasopharynx of other cases. There is no doubt that this virus, on occasion, does give rise to encephalitis. However, it is frequently found in Man and it may have been an accidental invader of the central nervous system. Although it naturally remains under suspicion, its role in causing encephalitis lethargica is in doubt. Indeed, most authorities are of the opinion that it is not the cause, which still remains to be discovered.

Ascending Myelitis due to B Virus.—A virus having some affinities with the virus of *Herpes febrilis* was isolated from the brain of a man dying of an ascending myelitis following the bite of a laboratory monkey. This virus is known as B virus. Sabin and Wright (1934) noted that it closely resembles the virus of herpes but has properties which distinguish it from that virus; thus it is pathogenic to rhesus monkeys, while the virus of herpes is not and, as Burnet and others (1939) concluded, the B virus has a more complex antigenic structure than herpes virus.

The laboratory worker concerned was bitten on the hand by an apparently normal monkey. Three days later he noticed an inflammatory reaction at the site of the bite with the formation of vesicles. Several days later he had cramps in the abdomen. He developed hyperæsthesia, and later flaccid paraplegia, and died of respiratory paralysis on the fourteenth day. This is the only case on record of an infection of Man due to this virus.

4. Encephalitis Possibly due to Viruses as yet Unidentified

A number of outbreaks of encephalitis have been reported from different parts of the world, where for various reasons a detailed investigation of their ætiology was not possible. These include cases in East Africa (Charters, 1940), Southern Rhodesia (Berney and Gelfand, 1946), England (Greenfield, 1943), and several other countries. It seems probable that viruses were responsible for many of these outbreaks and it is clear that still further additions will have to be made to this group of the virus encephalitides.

Virus Poliomyelitis (Inflammation of the Grey Matter of the Spinal Cord)

Poliomyelitis is a disease of increasing importance. It was known in ancient Egypt, but has only assumed epidemic form in the last hundred years. These epidemics first occurred in the countries where the standard of living and of hygiene was highest. The first extensive epidemic occurred in Scandinavia in 1868. Later, in 1894, epidemics occurred in the United States, later still in Australia and New Zealand. As other countries have attained comparable standards of living, they in turn have suffered from extensive outbreaks. During and since the recent war, epidemics have occurred in many regions of the world. Some experienced epidemics for the first time. England suffered the first widespread epidemic in the summer of 1947. There is reason to believe that often these epidemics followed the introduction of more than usually virulent strains of virus, particularly from the Middle East.

From studies made during the war, it is now clear that poliomyelitis is a world-wide disease and that infection is more widespread in the backward and primitive countries of the Tropics and Subtropics than in the more highly developed lands of Western Europe and North America. However, the incidence of the paralytic form is much higher in the latter. The most likely explanation for this appears to be that in their insanitary surroundings, primitive peoples come into contact earlier and more regularly with endemic strains of the virus, and so acquire an immunity not shared to the same degree by more highly civilized peoples. The former thus are able to resist infection with epidemic invasive strains of the virus better than the latter. Differences in the staple diet may also play a part, for it has been shown that experimental animals on a thiamine-deficient diet are more resistant to infection than the normal animals.

Obviously it is of the greatest epidemiological importance that the number of strains of virus causing poliomyelitis should be accurately known. A start has been made in answering this question. Recent work by Morgan (1948) indicates that these may be divided into two main groups, namely:

(*a*) Non-Lansing type strains, which besides Man cause disease experimentally only in the primates. Of the non-Lansing strains so far tested, all have been of one immunological type. Further tests may reveal more types.

(*b*) Lansing type virus strains which, in addition to primates, are pathogenic to certain rodents including cotton rats and white mice. All the strains of human poliomyelitis that have proved pathogenic to rodents have been found to be immunologically similar and of the Lansing type.

At the recent Conference in New York on poliomyelitis, held under the auspices of the National Foundation for Infantile Paralysis, it was decided that the name poliomyelitis should be restricted to these two types of virus. It was decided that the disease of mice caused by Theiler's virus, often called mouse-poliomyelitis, should be known by the name Theiler (1941) originally gave

it, namely spontaneous mouse encephalomyelitis. Although he realized that the virus and the disease it caused had many characteristics in common with the virus and disease of human poliomyelitis, he purposely did not call it mouse poliomyelitis. Unfortunately others did not follow his lead, and considerable confusion has resulted from the use of the term mouse poliomyelitis.

Confusion regarding the MM virus, usually called the MM strain of poliomyelitis, also exists. There is doubt as to its origin. In view of this it was decided that the MM virus, and similar viruses, should not be included in the poliomyelitis group. Recent work has added considerably to the interest of the MM virus. It has been shown to be immunologically similar to the virus of encephalomyocarditis, which was isolated from a dead chimpanzee in Florida (Warren, 1948). These viruses both cause a fatal encephalitis when inoculated intracerebrally in mice. Another virus, apparently of this group, was isolated by Dick and others (1948) from a paralysed monkey in the compound of the Yellow Fever Research Station at Entebbe. Similar viruses were then isolated from mosquitos and a mongoose caught in the area. The fact that Mengo virus was isolated from mosquitos on one occasion suggests, but does not prove, that these insects may have a part in its transmission. Then Dick himself became ill, with intense headache and fever, during which he developed nerve deafness and weakness of the trapezius. A similar virus was isolated from his blood. Neutralizing antibodies to this virus were shown to be present in his serum during convalescence. This virus has been named Mengo virus, after the province in Uganda where it was isolated. In more recent work Dick has shown that Mengo virus is closely related to the virus of encephalomyocarditis. The viruses thus discovered have been isolated from widely scattered points. It thus appears that this group of viruses may have a wide distribution in the world. How often they cause disease in Man is not yet known and whether the illness often simulates true poliomyelitis has not yet been determined. Dalldorf and Sickles (1948) recently isolated a filterable agent from the fæces of children during the acute phase of an illness resembling poliomyelitis. This agent produces paralysis and muscle lesions in suckling mice and hamsters but not in rhesus monkeys. Further reports will be awaited with interest.

The Spread of Poliomyelitis.—Although it is not yet certain how poliomyelitis is most commonly spread, a considerable amount of evidence has been collected in regard to the problem. In patients, the virus is found in the throat four or five days prior to the onset of symptoms and for three or four days afterwards. Apart from this limited period the virus has only rarely been detected in the throat, though in one investigation it was detected in two patients eleven days after the onset (Pearson and Brown, 1947). It is present in the fæces of most patients regularly for three weeks and in a small proportion for as long as eight weeks and, occasionally, for twelve weeks (Horstmann and others, 1944). Observations by Gordon and others (1948), and by Aycock and Kessell (1943) have indicated that the infectious period of cases extends from four days before to five days after the onset of symptoms. This period corresponds to the time when the virus is most commonly present in the throat. It suggests, then, that spread takes place from the throat virus. If fæcal virus were responsible for spread during contact, the period of infectiousness of a case would begin earlier and last longer than has been found to be the case.

However, the acceptance of the respiratory droplet transmission hypothesis leaves unexplained the remarkable seasonal incidence of poliomyelitis. Although winter epidemics have been described, epidemics in temperate climates occur almost always in the summer and autumn. This is the time of the year when known alimentary infective diseases like typhoid and dysentery are commonest, and also when insects and other arthropods are most prevalent. This naturally has raised the question as to whether poliomyelitis may not be an alimentary infective disease or an arthropod-borne disease, especially as abundant virus occurs in the fæces. The virus has been isolated a number of times from batches of flies, since Paul and others first demonstrated its presence in flies in 1941. The suspicion that flies may play a major role in the spread of poliomyelitis has been further strengthened by the recent observations of Melnick and Penner (1947) that, after feeding on infected human stools, the blowfly *Phormia regina* continued to excrete virus for two or three weeks. Under similar conditions Theiler's virus or inert carmine were detectable for three to five days only. These findings suggest that there may be a biological relationship between flies and the virus, though it still remains to be proved that the virus actually multiplies in the fly. However, there are so many clear instances of spread from human to human that there is general agreement that this is a common method of spread. It is not clear whether infection takes place by respiratory droplets or by hand-to-mouth contamination. There is also no doubt that of those infected only a minority develop symptoms, and still fewer develop paralysis. It has long been suspected that fatigue and violent

exercise predispose an infected individual to a paralytic attack. Ritchie Russell (1947) has confirmed this suspicion by his enquiry into the history of severely paralysed cases. This revealed that nearly all these cases had indulged in severe or prolonged exercise within a probably significant period before they became ill, or during the pre-paralytic stage. In contrast those who escaped with light paralysis or had non-paralytic attacks had been relatively quiet in the corresponding period.

There is also little doubt that operations on the throat shortly after or shortly before infection predispose an individual to a bulbar form of the disease. Extraction of teeth, and also carious teeth, may similarly provide a portal of entry for the virus, though there is little direct evidence to incriminate them.

Pathological studies of fatal human cases have revealed that the virus does not gain entrance to the central nervous system via the olfactory nerves and bulb. This is the route often taken in monkeys experimentally infected by intranasal instillation. The work of Faber and others (1948) suggests that the nerves of the throat may be especially implicated in human infections.

Prevention of Spread.—Experience has shown that all measures usually enforced—the isolation of cases, the closing of swimming baths and schools, and places of entertainment—have little effect in preventing the spread of poliomyelitis. To be of value, isolation would have to include all the members of each affected household, and the period would have to be extended from three to eight weeks. Such stringent isolation is usually not possible, and even when practicable is often unavailing. Indeed it could hardly be otherwise in a disease in which only a small proportion of those capable of spreading infection have symptoms of illness.

The only solutions to this problem appear to be the development of a prophylactic vaccine, or the discovery of a chemical or other agent which will either inactivate the virus or prevent its access to the susceptible nerve cells. Needless to say, intensive efforts are being made to develop a safe effective vaccine and also to discover a drug which will act prophylactically to prevent infection. It is to be hoped that these endeavours will soon be successful.

Diagnosis of Poliomyelitis.—There is no routine laboratory test yet available for the diagnosis of poliomyelitis. Attempts have been made, and are being continued, to develop complement fixation and flocculation tests. There is a great need for such diagnostic tests, and it is to be hoped one will soon be developed. At present the only laboratory method of determining whether an illness is or is not poliomyelitis is by demonstrating the virus by the inoculation of monkeys. The materials usually tested are throat washings taken from the patient within three days of onset, or more certainly, fæces collected within three weeks of onset or, in fatal cases, suspensions prepared from the spinal cord and brain stem. Fortunately, paralytic poliomyelitis is readily diagnosed on clinical grounds though a number of conditions may cause confusion. One of the most difficult to distinguish from poliomyelitis is polyneuronitis, or the Guillain Barré syndrome. This syndrome is generally assumed to be due to a virus, though its presumptive virus has not yet been isolated. Clinically, after an interval of three to six weeks following an upper respiratory infection, the patient develops weakness and paralysis of various groups of muscles, usually symmetrical in distribution. If not fatal because of involvement of the respiratory muscles as it sometimes is, recovery from the paralysis is usually complete. It is, therefore, important in giving a prognosis to be able to differentiate this condition from poliomyelitis. This can be done by the examination of the cerebrospinal fluid. In the Guillain Barré syndrome there is an increased protein content, but there is no increase in the number of cells. In poliomyelitis the protein and the cells are both increased. In the early stages neutrophils form a large proportion of the cells, later lymphocytes predominate. In the recovery stage, however, the cell count may return to normal, whereas the protein content remains elevated for a longer time.

Two cases of infectious mononucleosis associated with ascending paralysis indistinguishable from that of the Guillain Barré syndrome have been described (Ricker and others, 1947). Both ended fatally. Post diphthertic neuritis may closely resemble the Guillain Barré syndrome. Differentiation depends on the demonstration of diphtheria bacilli and on the relatively slight elevation of the spinal fluid protein. Similarly in four cases of polyneuritis associated with the ingestion of large amounts of sulphonamides over long periods, there was no elevation of the total protein level in the spinal fluid (Hand and Rudoy, 1948).

It is also of great importance from the point of view of prognosis to be able to distinguish poliomyelitis from encephalitis lethargica. The ultimate prognosis in encephalitis lethargica may be serious even though the acute attack has been mild and the patient apparently fully recovered, for about half the surviving cases later develop sequelæ, most

frequently Parkinsonism. On the other hand, in poliomyelitis the maximum involvement usually occurs within forty-eight hours, and nearly always within one week of the first recognition of paralysis. Thereafter any change will be for the better. This differentiation in routine practice has to be made on clinical findings and is sometimes very difficult.

Comparing the pathological pictures of encephalitis lethargica, Japanese B encephalitis, and poliomyelitis, Scheinker (1948) noted a similarity of the essential pathological features, namely a primary involvement of the nerve cells of the grey matter, predominantly focal in character and accompanied by focal proliferation of microglia cells with the formation of glial nodules. The differentiation of these diseases is based chiefly on the distribution of the pathological lesions. In cases of Japanese B encephalitis, the cerebral cortex, the thalamus, and the substantia nigra are most severely affected. The lesions of the cerebellum, the medulla, and the spinal cord, are discrete and inconstant.

In human poliomyelitis the brunt of the morbid process is borne by the nerve cells of the grey matter of the spinal cord, and of some of the cranial nerve nuclei of the medulla and the midbrain. The lesions of the pons, the cerebellum, and the basal ganglion are discrete and not constant. The cerebral cortex is often spared.

In encephalitis lethargica the lesions are found particularly in the basal ganglia and the substantia nigra. Discrete focal lesions may be seen in the midbrain and pons ; they are as a rule absent from the cerebral cortex, the cerebellum, and the spinal cord.

SECONDARY VIRUS ENCEPHALOMYELITIS

Several familiar, usually non-neurotropic, virus diseases of Man may be complicated by involvement of the central nervous system. This complication is rare but appears to be increasing in incidence. It has been described as following dengue, herpes febrilis, herpes zoster, infective hepatitis, influenza, lymphogranuloma inguinale, measles, mumps, rubella, sandfly fever, variola, and varicella. Although the primary diseases are quite different, the signs and symptoms of the nervous involvement are essentially similar, and appear one to two weeks after the onset of the primary illness. There is a recrudescence of fever with a sudden onset of meningitic and cerebral signs and symptoms, including convulsions in small children, headache, neck rigidity, vomiting, a dulled intellect, drowsiness, stupor increasing to coma, and paralysis usually affecting the cranial nerves and often resulting in squints.

The blood shows a polymorphonuclear leucocytosis. The cell count of the cerebrospinal fluid is increased up to 50 to 500 cells, mostly lymphocytes, per c.mm. The protein content is raised.

The severity of the post-infective encephalitis bears no relation to the severity of the preceding exanthem. The prognosis appears to vary somewhat with the different primary diseases. In mumps, which occasionally present as encephalitis, it is excellent for almost all cases make a complete recovery. In measles, in which there appears to be an increasing incidence of encephalitis, for in Chicago in 1937–8 it was 1 in 15,000 cases whereas in 1946 it occurred as frequently as 1 per 642 cases (Hoyne and Slotkowski, 1947), the mortality rate is from 10 to 15 per cent. In chickenpox, in which encephalitis often assumes a cerebellar ataxic form, the prognosis varies but is often grave (Forman, 1946).

In clinical symptoms and pathology post-infective encephalitis has many resemblances to post-vaccinial encephalitis. Although isolated cases had occurred and been described before then, this condition first attracted general attention in 1922–3, when it assumed serious proportions. It is now recognized as one of the most serious risks to be taken in vaccinating against smallpox. The incidence varies in different parts of the world. It assumed particularly alarming proportions in Holland, where it was the custom to vaccinate children just before going to school. The condition is rarely seen in infants under two years old. When it occurs it nearly always follows primary vaccination and is rarely seen following second or later vaccination.

The first symptoms develop ten to thirteen days after vaccination ; most cases begin on the twelfth day. The child suddenly becomes ill, with fever, headache, vomiting, occasionally convulsions, squints, and drowsiness progressing to coma, and in from 30 to 50 per cent. of cases to death. The blood shows a neutrophil leucocytosis and the cerebrospinal fluid an increase in cells up to 100 to 200 per c.mm., mostly lymphocytes and mononuclear cells. At necropsy the meniges are congested, and microscopically there is a mild inflammatory reaction with infiltration of lymphocytes, plasma cells, and endotheloid cells. The brain substance shows congestion and areas of softening. Microscopically the outstanding feature is wide perivascular demyelinization, especially round the veins. There is slight perivascular infiltration of inflammatory cells and also a diffuse cellular infiltration of the brain substance. Hyaline thrombi may be seen in the blood vessels. The nerve cells are usually well preserved. In general, the white matter is more affected than the grey.

Occasionally encephalitis has followed vaccination against yellow fever with a substrain of the avirulent 17D strain, or with the French neurotropic strain (Fox and others, 1942). These cases nearly all recovered.

As post-infective encephalitis and post-vaccinial encephalitis have similar pathological lesions, it is probable they have a similar ætiology. Several theories have been advanced to explain their development. It has been suggested that it is an inflammation due to the virus itself, or that it is an activation of an encephalogenic virus already present. The most likely explanation is that it is what might be termed an auto-allergic reaction to virus combined with some constituent of the nervous tissue.

The neuroparalytic accidents following therapeutic rabies vaccination may be discussed with advantage at this stage. In a small but apparently increasing proportion of cases treated by multiple injections of inactivated virus in central nervous system tissue, a serious nervous involvement occurs. This usually develops late in the course of injections, most commonly between the twelfth and fifteenth day of treatment. Clinically the condition commonly assumes a dorso-lumber type. The patient has fever and the lower limbs become paralysed. There is often paralysis of the sphincters as well. The death rate of this form is about 5 per cent. In some cases it assumes a Landry type and, following paralysis of the lower limbs, the upper limbs are affected, later the face. In this form about one-third of the cases die.

In the neuritic type, the patients have fever during which they develop paralysis of one or more of the cranial nerves.

In those cases that recover, recovery is usually complete. It has been stated that demyelinization is not an outstanding feature of the post-mortem findings, although most authorities consider that this condition is closely related to post-vaccinial encephalitis.

Experiments carried out by Kabat and others (1947) and Morgan (1947) support the hypothesis that post-infective and post-vaccinial encephalomyelitis may be regarded as auto-allergic or auto-antigen-antibody reactions to some component of the central nervous system tissue made auto-antigenic by the presence of virus. The neuroparalytic accidents following anti-rabies vaccination may similarly be regarded as reactions due to the development of antibodies to this component, following the injections of nervous tissue.

In these experiments a picture resembling acute disseminated encephalomyelitis in the human being was produced regularly and rapidly in rhesus monkeys by injections of emulsions of homologous monkey brain administered with an adjuvant, paraffin oil, in which heat-killed dried tubercle bacilli were suspended.

Morgan noted that positive reactions occurred only in response to central nervous system tissue containing white matter. An analysis of the results suggests that the antigen concerned is the myelin of the white matter of central nervous system.

It is interesting to speculate whether a number of other obscure conditions of the central nervous system like disseminated sclerosis, many drug encephalopathies, amyotrophic lateral sclerosis, Schilder's disease, and others, may not be manifestations of similar auto-antigen-antibody or auto-allergic reactions. This, however, is a large subject and merits full discussion on its own.

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CHARLES DENISON, M.D.
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FOURTH INTERNATIONAL NEUROLOGICAL CONGRESS
PARIS, SEPTEMBER 5 to 10, 1949

The Fourth International Neurological Congress will be held in Paris from Monday, Sept. 5 till Saturday, Sept. 10, 1949.

Scientific business will comprise discussions upon four main topics: (1) the thalamus and its pathology; (2) electroencephalography and electromyography; (3) virus diseases of the nervous system; (4) the surgery of pain. The official openers of these four topics have already been nominated by the various National Vice-Presidents. Members of the Congress can participate in the discussion, their remarks being strictly limited to five minutes each.

Short papers on any neurological topic will also be given, and members are invited to submit titles and an abstract of their communication to the Secretary by Feb. 1, 1949. The length of the communication must not exceed ten minutes. No member may give more than two communications.

It has been decided by the General Committee of the Congress that application for membership and all financial contributions must be made through a National Committee for each country, which will transmit all applications for membership and all subscriptions to the General Committee in Paris. The British National Committee has been constituted by the Section of Neurology of the Royal Society of Medicine, and is as follows: *President*, Dr. Anthony Feiling; *Secretary*, Dr. Macdonald Critchley; *Treasurer*, Dr. M. J. McArdle, *Other Members*, Drs. Douglas McAlpine, W. Ritchie Russell, and G. Smythe, and Sir Charles Symonds.

There are two classes of members: (1) full members, i.e., all medical men or women interested in neurology, and (2) associate members, i.e., non-medical men or women interested in the Congress.

Every member of the Section of Neurology of the Royal Society of Medicine is earnestly invited to contribute the sum of 10*s.* towards the general expenses of the Congress (whether attending or not). The subscription for full members is £2 10*s* 0*d.* and for associate members £1 5*s.* 0*d.* All cheques should be made payable to and sent to Dr. M. J. McArdle, 58a, Wimpole Street, London, W.1, before April 1, 1949.

Details as to hotel accommodation will be published later. The local committee of the Congress have appointed the American Express Company to be the official travel agents.

BOOK REVIEWS

Critical Studies in Neurology. By F. M. R. Walshe. 1948. Edinburgh: E. and S. Livingstone. Pp. xxv.+ 256. Price 15*s.*

Dr. Walshe's critical writings and orations of recent years are well known to neurologists. In this volume six of his papers are republished in a well-produced little volume. Some may from time to time have regretted the almost vitriolic words of comment used by Dr. Walshe to disagree with the hypotheses of some well-known physiologist, but none can fail to acknowledge the great educational value to the young neurologist of reading, or preferably hearing, Dr. Walshe's expositions. To quote from the foreword, "A prime purpose of this reprint therefore is to stimulate critical thinking amongst postgraduate students of neurology who may wish to penetrate more deeply into one or other aspects of this fascinating branch of medicine, and, when they sit down before the literature, to make of them gourmets rather than gourmands." The training of the critical faculty was never more required than it is today, for our minds tend to be overwhelmed by the stream of new knowledge. Dr. Walshe exemplifies the critical spirit, and though the young neurologist can rarely hope to emulate his remarkable choice of words, he should endeavour to train himself to understand some part of neurology so well that he can criticise research studies on at least some aspects of his speciality with the confidence and clarity of thought and expression which he will find in these papers.

The Skull, Sinuses, and Mastoids: A Handbook of Rœntgen Diagnosis. By Barton R. Young. 1948. Chicago: The Year Book Publishers Inc. London: Messrs. H. K. Lewis. Pp. 328. Illustrated. Price 36*s.*

It is unfortunate that neuro-radiology is often relegated to the position of being a branch of bone radiology. Dandy introduced pneumo-encephalography thirty years ago, and it is over twenty years since Moniz began carotid arteriography. When properly combined these methods of investigation, together with the straight radiography of the skull, probably provide information more accurate and yet more diverse than can be obtained from any other branch of diagnostic radiology. This is the main fascination of the subject. Radiographing the "dry bones" of the head seldom provides the whole radiological answer, and should be only a prelude.

In its limited sphere, however, this little "Handbook of Rœntgen Diagnosis" covers the ground well. It is

the sixth of a series of similar handbooks. The arrangement consists of text on one side of the page and radiographic reproductions on the other. The latter are of good quality. There are three sections (1) skull, (2) sinuses, and (3) mastoids. The first part occupies half the book and is of most interest to neurologists. The appearances of the normal skull are well described and, equally important, the commoner normal variations and physiological intracranial calcifications are listed. Concise descriptions of pathological conditions follow, nearly all of which are well illustrated. There is one surprising statement on page 140: "Approximately 42 per cent. of brain tumours are metastatic." One feels that this must be a misprint.

Headache and Other Pain. By H. G. Wolff, M.D. 1948. New York: Oxford University Press. London: Geoffrey Cumberlege. Pp. 642. Price 63*s*.

No physician or surgeon who treats patients complaining of headache or other pains in the head, face, or neck should neglect to study this important monograph.

Dr. Wolff's clinical researches are well known to neurologists but their importance can hardly have been fully appreciated prior to the appearance of this remarkable record of work carried out during the past fifteen years.

Being a practising neurologist and psychiatrist, the author brings to his research work a refreshing "vision" which is lacking in many contemporary studies of pain and other forms of sensation. He turns readily to the clinical lesion to help him in his work. For example he studies lumbar puncture headache in patients with one trigeminal nerve sectioned, and the pain of muscle spasm in a patient with tetanus. The subjective effect of irritating almost every cranial structure is studied, including the meninges, blood vessels, eye muscles, nasal mucosa and sinuses, scalp and neck muscles, and teeth. For example a temporal headache may be produced by electrical stimulation of a tooth, and partly relieved by the injection of procaine into the scalp in the temporal region.

Among the phenomena described are the temporary abolition of migrainous scotomata by a vasodilator, the influence of a vasodilator on some features of tic douloureux, and the modification of many atypical facial pains by pressure on the external carotid artery. The chapter on the personality features in persons with migraine, and the treatment of these cases is of great practical value to the physician and psychiatrist.

Some of Dr. Wolff's conclusions are based on evidence which other research workers may consider to be inadequate, but to the reviewer's mind his somewhat challenging method of expressing his own convictions is both justifiable and stimulating: it is easy for the intelligent reader to see where the evidence is somewhat tenuous, and in time most of Dr. Wolff's conclusions will probably be proved correct.

The Quarterly Journal of Experimental Psychology. 1948. Cambridge. W. Heffer and Sons. Volume I, Part I. £1 10s. per annum.

We welcome this new journal which is published for the experimental psychology group, with Mr. R. C. Oldfield as editor. It should provide much needed facilities for the publication of research work being conducted by experimental psychologists. The contents of the first number are as follows:

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Normal and Abnormal Psychology. By J. Ernest Nicole. 1948. London. George Allen and Unwin. Pp. 95. Price 6*s*.

This book is described by the author as a précis written largely for mental and general trained nurses and for junior students who require some elementary knowledge of psychology. It would, therefore, be unfair to make excessive demands. The comprehensive title is, however, apt to mislead, since only those schools commonly called "dynamic" receive any mention, and a large part of the book is taken up with a popular and inevitably over-simplified presentation of the Freudian point of view. Brief reference is made to other analytic schools and to the views of McDougall. Much emphasis is placed on the psychogenetic aspects of mental disorder, and there is a chapter on so-called psychosomatic medicine. No doubt this book presents the kind of psychology the general public expects, but to the medical reader it is of little interest.

Psychology of Personality. Ross Stagner. New York. McGraw-Hill Book Co. 1948. Second Edit. Pp. xiii +485. Illustrated. Price 30*s*. net. U.S.A., $5.00.

In present-day psychological writings there is an unfortunate tendency for length to vary inversely with knowledge. The present book is no exception to this rule. Although the scientific study of personality is in its infancy, Professor Stagner has devoted what may seem to some of us a disproportionately long book to its growing pains. Nevertheless, he has performed a most useful service in drawing together a mass of material bearing on personality drawn from experimental, clinical, and anthropological sources. This material is assembled with judgment and skill, and the result may be confidently recommended to anyone who wishes to gain a broad indication of the contemporary outlook in this most difficult field of psychology.

To the neurologist, the most interesting parts of Professor Stagner's book will probably be those concerned with the organization of temperament and character. On the basis of a careful appraisal of the available data, the author evaluates in a sensible way the respective importance of constitutional, physiological, and environmental factors in the formation and growth of personality. It is a pity, however, that he devotes practically no space to personality changes associated with injury or disease of the nervous system. Even the fashionable topic of prefrontal leucotomy is dismissed in eighteen lines. Nevertheless, much of what Professor Stagner has to say regarding problems of personality in general should be of value to anyone who aspires to bring order into the confusing realm of contemporary neuropsychiatry.

Le Système Nerveux Végétatif. By G. and C. Tardieu. 1948. Paris: Masson et Cie. Pp. 742; 3 figures. Price 1950 fr.

This book is not, as its title might imply a straightforward textbook of the autonomic nervous system Although it opens with sections on anatomy and physiology, its main theme is the development and application to clinical medicine of the experimental work of Reilly and his colleagues in France on "irritation" of the autonomic system. These workers found that the response to intense and prolonged stimulation of autonomic nerves or centres differed entirely from the response either to a less intense and more physiological stimulus or to section of the same pathways. They named this third type of response "l'irritation nerveuse." The essence of the response was an immediate and very marked vasodilatation, which in experimental animals was often irreversible and if widespread led to death. Thus "irritation" of the diencephalon produced a generalized effect, characterized by cerebral œdema, increased respiration, hypertension, pulmonary œdema, and albuminuria or hæmaturia with gastro-intestinal hæmorrhages. Local responses could also be elicited, as, for instance, that from splanchnic nerve "irritation," which caused œdema of the gut with swelling and hæmorrhage from Peyers patches, and albumin or sometimes blood in the urine. In these autonomic responses the authors of this book see possible mechanisms for the signs and symptoms of many bodily diseases. The major part of the book consists of collating disease processes, both local and general, with these responses; and in this connexion allergy and anaphylaxis, nephritis, gastric ulceration, asthma, coronary disease, and the acute manifestations common to severe zymotic diseases are all discussed.

The conception of pathways and centres in the central nervous system, which may mediate some of the manifestations of all disease, has already been explored to some extent by Speransky; and the book under review, though limited to the autonomic system, is reminiscent of his approach. The idea has a logic of its own, since the nervous system shares with the blood the attribute of supplying every tissue in the body.

This book should certainly be read by those interested in the mechanics of disease processes. The authors have gathered together a large number of interesting facts, many of them, the result of M. Reilly's researches, which are little known over here and which, though his experimental procedures will certainly be criticized by neurophysiologists, may be of value to neurologists and neurosurgeons. Those educated in the traditions of English medicine will be chary of accepting the wider implications that the authors draw, even though they may, in fact, be describing a fundamental mechanism in the pathogenesis of disease.

The style of the book is turgid and the method of presentation causes much irritating repetition of information. The sections on anatomy and physiology are by no means exhaustive. Thus, scant attention is paid to autonomic pathways or functions above diencephalic level. This may have been wise restraint a year or two ago, but it will certainly require revisions in the near future.

Anatomia Funcional del Sistema Nervioso Vegetativo. By Ramon Lopez Prieto and Francisco Garcia Uria. 1947. Valladolid. Tipografia "Cuesta." Pp. 172 + vi; 43 illustrations. Price 58 pesetas.

This is a clear resumé of the anatomy of the autonomic nervous system, including work of modern authors. It will be of use to students and practitioners alike. It is well illustrated with drawings and clear diagrams. Although authors and a few dates are mentioned, unfortunately the lack of bibliography is a limitation.

L'Axe Corporel, Musculature et Innervation. Etude Anatomique, Physiologique et Pathologique. By André-Thomas and J. de Ajuriaguerra. 1948. Paris: Masson et Cie. Pp. 538 with 143 figures. Price 1,650 fr.

This comprehensive book contains four sections. The first is concerned with physiology and includes a study of the movements observed in the human infant soon after birth, and of postural reflexes, the effect of gross cerebral lesions, and the distortions of posture caused by focal epilepsy or electrical stimulation of the brain. The second section analyses the muscular disorders resulting from disease of the muscles, nerves, spinal cord, and brain. The muscular dystonias are considered in special detail. Disorders of the ocular movements in disease are considered in part 3. This publication brings together much of what is known regarding motor functions and their disorders as seen in the clinic. It should be a useful work of reference for the neurologist and neurophysiologist, but unfortunately the quoted references can only rarely be identified, and there is no index to the volume.

Actualités de Neuro-Chirurgie. By G. Guiot. 1948. Paris. G. Doin et Cie. Pp. 84. 57 illustrations. Price 450 francs.

This book gives an account of work published by the author in the French press and of the ideas inspiring the school of the late Clovis Vincent. The following points are of interest: in the section dealing with cerebral pathology, the description of the "corneo-pterygoid reflex" (contralateral deviation of the mandible on coarse stimulation of the cornea) observed in severe lesions of the upper brain stem, such as occur with a temporal pressure cone; the use of lipiodol (1/3 c.cm.) in ventriculography for precise localization of obstructions of the aqueduct of Sylvius; observations on the most convenient sites for burr holes in intracranial hæmorrhage; and the distinction between "passive" and "active" cerebral œdema. In the third section, on treatment, the author's suggestions of dealing surgically with the temporal pressure cone by his own sub-temporal approach, the anatomy of the venous drainage in the middle fossa, mesencephalic tractotomy, and intervention on the interpeduncular cistern (with reference to streptomycin therapy) deserve the neurosurgical reader's attention.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received)

New Fields of Psychiatry. By David M. Levy. 1947. London: Chapman and Hall: New York: W. W. Norton. Pp. 171. Price 12*s.* 6*d.*

Introduction to Group-Analytic Psychotherapy. By S. H. Foulkes. 1948. London: William Heinemann Medical Books. Pp. xiv+181. Price 21*s.*

Contributions to Psycho-Analysis 1921-1948. By Melanie Klein. London: The Hogarth Press and the Institute of Psycho-Analysis. Pp. 416. Illustrated. Price 21*s.*

Psychiatry in General Practice. By M. W. Thorner. 1948. Philadelphia and London : W. B. Saunders Co. Pp. xi+659. Price 40*s*.

Psychiatry : A Short Treatise. By W. O'Connor. 1948. Bristol : John Wright and Sons. Pp. 380. Price 35*s*.

Sex Problems in School. By René Allendy and Hella Lobstein. 1948. London : Staples Press. Pp. 182. Price 10*s*. 6*d*.

The Alcoholic Woman. By Benjamin Karpman. 1948. Washington : Linacre Press. Pp. xv+256 with diagrams. Price $3.75.

Public Mental Hospitals in England and Wales : a Survey. By Dallas Pratt. 1948. Philadelphia : National Mental Health Foundation. London : H. K. Lewis. Pp. 38. Price $0.50.

Biological Reactions Caused by Electric Currents and by X-rays. By J. Th. van der Werff. 1948. Amsterdam : Elsvier Publishing Co. Inc. London : Cleaver-Hume Press Ltd. Pp. xii+203, with diagrams. Price $5.00 or 30*s*.

Neurological Anatomy in Relation to Clinical Medicine. By A. Brodal. 1948. Oxford : Clarendon Press. London : Geoffrey Cumberledge. Pp. xv+496, illustrated. Price 42*s*. (A revision and translation of " Neuro-Anatomi," published in Oslo, 1943.)

Clinical Examination of the Nervous System. By Monrad Krohn. Ninth Edition. 1948. London : H. K. Lewis. Pp. xx+459, illustrated. Price 16*s*.

Atlas of Neuropathology. By W. Blackwood, T. C. Dodds, and J. C. Somerville. 1949. Edinburgh : E. and S. Livingstone. Pp. xi+199. Illustrated. Price 35*s*.

Trabajos del Instituto Cajal de Investigaciones Biológicas, Tomo 38. 1946. Madrid : Instituto Cajal. Pp. 231. Illustrated. No price given.

Sexual Disorders in the Male. By Kenneth Walker and Eric B. Strauss. 1948. Third Edition Revised and Enlarged. London : Hamish Hamilton Medical Books. Pp. 260. Price 15*s*.

Transactions of the Ophthalmological Society of the United Kingdom, vol. 66, 1946. 1947. London : J. and A. Churchill. Pp. lvx+691. Illustrated. No price given.

Lehrbuch der Neurologie und Psychiatrie. By Gottfried Ewald. 1948. Second Edition. Munich : Urban and Schwarzenberg. Pp. 478. With illustrations, some in colour. Price DM32.

Die Elemente der Nervösen Tätigkeit. By A. E. Kornmüller. 1947. Stuttgart : Georg Thieme Verlag. Pp. 120. Illustrated. Price DM13.50.

Thromboendangiitis Obliterans des Gehirns. By F. Llavers. Basel : Benno Schwabe. Pp. 248. Illustrated. Price Sw. fr. 24.

Klinische Electroencephalographie. By A. E. Kornmüller. 1944. Munich and Berlin : J. F. LeRomanns Verlag. Pp. 147, illustrated. Price DM14.

Du Réflexe au Psychique. By Paul Cossa. 1948. Bruges : Desclée de Bronwer. Pp. 288, illustrated. Price 125 fr.

Etudes Psychiatriques. By Henri Ey. 1948. Bruges : Desclée de Bronwer. Pp. 261. Price 200 fr.

Epilepsies. By L. Marchand and J. de Ajuriaguerra. Bruges : Desclée de Bronwer. Pp. 724. Price 475 fr.

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"INTEGRATION, THEN AND NOW"*

BY

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Oxford

My title implies an incursion into history which has for its landmark Sherrington's "Integrative Action of the Nervous System." Those Silliman lectures (Sherrington, 1906) given at Yale University now more than forty years ago, have ever since been a beacon in the voyage of neurological discovery. The definition of "integration" cannot be made in one sentence without preface. Sherrington's emphasis on the cell will be remembered. "Nowhere in physiology," he said, "does the cell theory reveal its presence more frequently than at the present time in the study of nervous reactions." Nerve cells have special properties as well as general. They have their own metabolic life like any other cell. They transmit states of excitation. By virtue of that property they integrate behaviour in a multicellular animal, binding its cells into a functional one and whole. That is Integration. But there are other kinds of Integration, as well as the nervous. There is the mechanical combination of unit cells and their chemical combination by endocrines. Nervous Integration is marked for its high speed of reaction and its nicety of adjustment in time and in space. To the clinical observer, Integration is an accepted reality. The whole human animal, integrated by its interdependent systems of nervous activity, blood supply, nutrition, and so forth, with Mind on top of all, can be and often must be studied as a whole, with all the advantages (or disadvantages) of the subject's co-operation. In the laboratory, where isolated phenomena are sought, the very nature of Integration makes isolation difficult because Integration is all-pervading. At every stage of analysis, integrated processes or actions hold a veil against the analysing gaze of the experimenter and resist his penetration. In support of this statement I propose to give a few examples from the history of experimental analysis.

Experimental Analysis

When the "Integrative Action" was published in 1906, unitary studies of cells were technically impossible. On the other hand, to illustrate the welding, the integration of nervous function, and yet to take from it some complications which could cloud close scrutiny, Sherrington chose for his picture the scratch reflex. Here is his canvas—a spinal cord isolated from high-level influences. That leaves a field for studying nervous integration at low levels. In this reflex no less than thirty-six muscles take part. The number of nerve cells, nerve fibres, and muscle fibres here integrated in allied reflex arcs is very large. They are integrated together and work together for the benefit of the whole organism in order to achieve quietus from skin irritation. As for the stimulus, the flea, we must have a controllable agent. Natural fleas being out of the question, one seeks a substitute. Mechanical stimuli such as a toothed wheel run over the surface of the skin are excellent provokers of the scratch. The end-organ in the skin, what Pavlov would later have called an analyser, can be activated by the electric current which, though less effective than the toothed wheel, is more easily controlled and more certainly repeated.

In passing, let us note that so far electrical stimulation of the bared afferent nerve has not been found to elicit the scratch. The analysing organ in the skin is the needed intermediary. In cataloguing the features of this widely engaging reflex, there is to be remembered for contrast the speed as well as the fatality of a simple nerve-muscle preparation when stimulated directly by its motor nerve. In a nerve-muscle preparation, the response comes rapidly if at all. From what is known of the speed of impulses along nerve-axones, the nerve-paths could carry them from the receptor to the effector in less than a score of milliseconds. But when the electric flea, in the form of a sharp slender pin connected to an inductorium, bites just gently, its modest titillations may sum during as long a period as three and a half whole seconds before the scratching response begins. Here then (but where exactly?) we have a summation of

*A lecture delivered at the National Hospital, Queen Square on Oct. 28, 1948.

stimuli. After that begins the impressive display of integrated movement among all the muscle masses causing rhythmic up-and-down movement of the limb. Moreover, the rhythm itself when reasonably extensive, has a steady rate in a fairly large dog at five beats a second. This vast organization of purposive movement has no counterpart in the spinal nerve-cell observed isolatedly.

If we travel forward in time to recent experiments by Eccles we see the behaviour of spinal nerve-cells subjected to excitation. They respond almost at once, within 0·2 to 0·3 milliseconds of the onset of

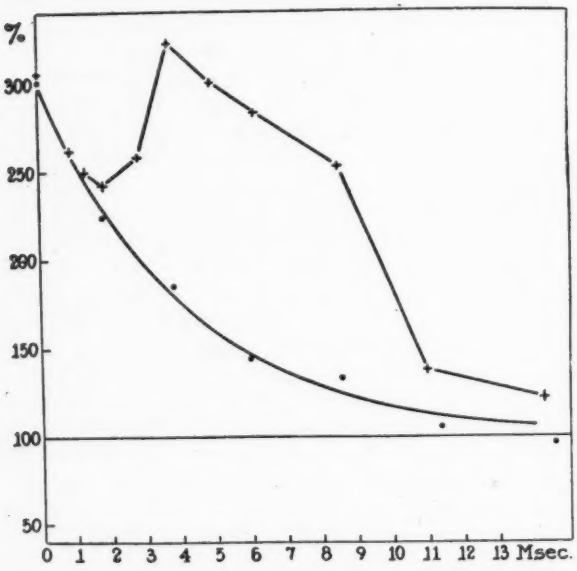

FIG. 1.—After Lloyd, 1946. *J. Neurophysiol.*, **9**, 426. Lower curve, filled circles, exponential regression of facilitation in flexor and extensor spinal nuclei. The test reflex is the maximum response in a two-neurone arc attainable by stimulation of a particular afferent nerve. The facilitating stimulus is a near-threshold shock applied to large fibres (12–20 μ) in a closely-allied afferent nerve.

Upper curve, crosses, similar but after slightly stronger facilitating stimuli, so engaging smaller afferent fibres, with the result that internuncial neurones (and indirect paths) come into play.

(This and Fig. 3 are published by kind permission of the author, the Editor of the *Journal af Neurophysiology*, and Messrs. Charles C. Thomas.)

the electrically polarized state which betokens excitation (Eccles, 1946). They remain in a diminishingly polarized state for less than a score of milliseconds.

Lloyd, working in the same field, finds that the excitation, evidenced by an electric charge on the cell, has declined to one-half in a mere 2·8 milliseconds (Fig. 1, lower curve). Thereafter excitation continues to decline logarithmically and is extinct

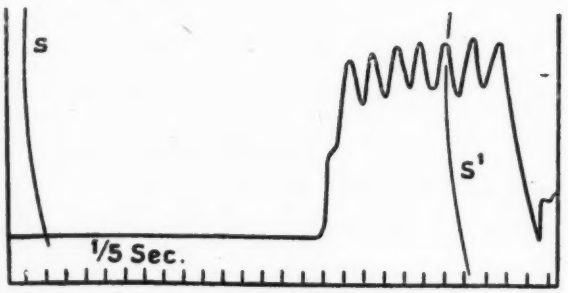

FIG. 2.—After Sherrington, "Integrative Action of the Nervous System," New Haven and London, 1906. The reflex response (scratch reflex) is latent, here only for 2·8 seconds, in spite of repeated "flea bites." (This and Fig. 4 are published by kind permission of the author and Messrs. Constable and Co.)

after 13 milliseconds (Lloyd, 1946). The functional closeness of helps to facilitation can be seen when a slightly stronger stimulus, engaging more (and smaller) nerve fibres is applied to the facilitating nerve. The crest of facilitation in the nerve centres is established for a second time (Fig. 1, upper curve). How different a time-chart is this in contrast to the scratch-reflex. The summation period in the latter, which may be as much as 3·5 seconds, indicates a high degree of complexity, a long chain of interneurones passing excitation from one to another (see also Fig. 2). As for the rhythmic muscular action, so characteristic a feature of the scratch reflex, we do not derive much information from observations on units of tissue, though one can glimpse the quick change from excitation to inhibition, the functional nearness of inhibition to

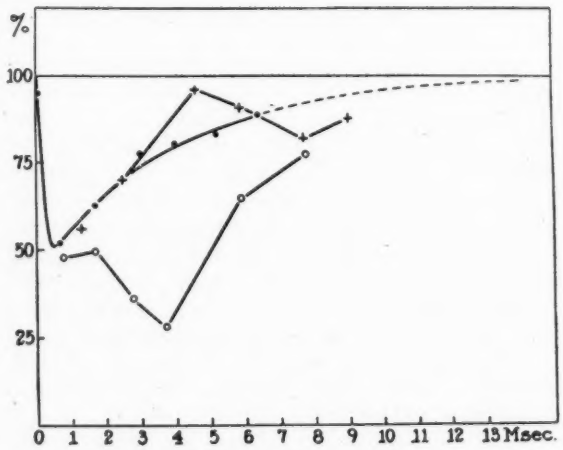

FIG. 3.—Primary inhibition in an extensor nucleus (middle curve, filled circles), admixed with secondary inhibition (lower curve, hollow circles) and excitation (upper curve, crosses) from internuncial activity. (After Lloyd, 1946.)

excitation, by turning again to Lloyd's records (Fig. 3). The die-away curve of inhibition is the mirror-image of excitation, but by engaging a few more nerve-fibres, by using stronger stimuli, inhibitory influences are annulled and quickly replaced by excitation. Here seems to be, as yet not too clearly focused, a paradigm of the swing from excitation to inhibition, and back again, in the vastly integrated reaction of the scratch reflex. The secret of rhythm is not to be seen in experimental simplicity, so integrated and therefore so complex is its nature. Attempts at analysis and simplification mean, at present, just destruction of the mechanism.

After-discharge.—You will remember that after-discharge, long-continued and rhythmic, is a striking feature of the nerve-cells and nerve-paths concerned in the scratch reflex. Sherrington reported that, for example, after 0·5 seconds of biting, a scratch developed which continued for 2·0 seconds (see also Fig. 4). Again how different is this integrated reflex from the reaction of a single cell or axone. We have a guide but no exact measure of the difference between the two. Of the internuncial paths and neurones engaged in these long-drawn-out effects we have little accurate knowledge.

The Compounding of Reflexes.—Sherrington reminds us that the simple reflex, without internuncial engagement, is " probably a purely abstract conception because all parts of the nervous system are connected together." " The main secret of nervous co-ordination," he said, " lies in the compounding of reflexes. Every reflex is an integrated reaction." It is a common cliché, and true, that " posture follows movement like a shadow." Limb movement can be initiated for example by messages from the pyramidal tract or by messages reaching the spinal cord at its own level, as in the flexor or crossed extensor reflex. But as we know now from Lloyd's work, the messages in those two cases are very different from the direct path of big nerve axones engaged in the postural reflex (Lloyd, 1941). In the former two cases the messages have an anatomically different path in which lie more than one synapse. In posture, only one synapse is concerned, and that at the ventral horn cell itself. Yet in the muscle, in spite of these differences between nerve paths, " every movement begins in posture and ends in posture." The take-over from posture to movement is smooth, the return from movement to posture is smooth.

In locomotor ataxia we see a state of affairs when the absence of correlation between movement and posture is strikingly illustrated. That picture needs no further mention. The close correlation of posture to movement, of static to phasic contraction, is well seen in the laboratory by testing the stretch-reflex response after a brief elicitation of the crossed extensor response. The stretch reflex is found to be much enhanced by the previous elicitation of crossed extension reflex and the enhancement continues to be marked, though to a diminishing degree, for 60 seconds or so (Liddell and Olmsted, 1929). Whether the same or kindred neurones are employed in the two reflexes we do not know. But the co-operative correlation in the two muscle responses is clear enough, and implies close correlation, if not the same identities, among the final neurones.

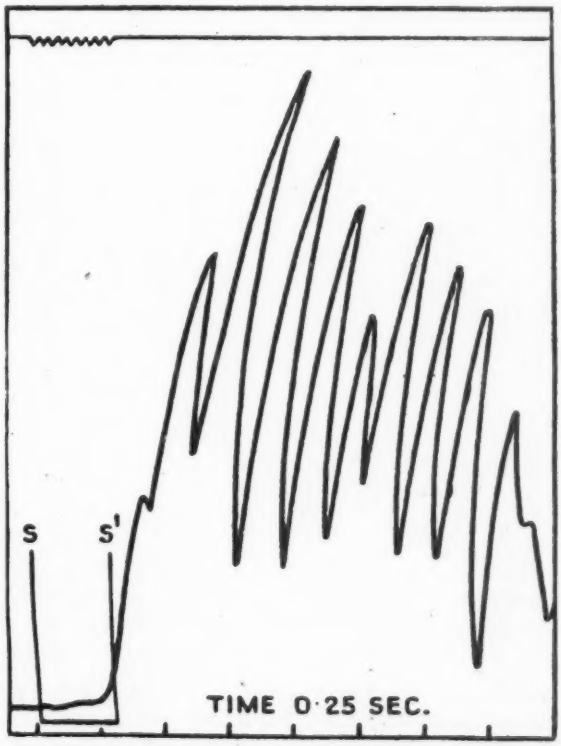

FIG. 4.—After Sherrington, 1906. The " flea " bites here for 0·25 sec. between S and S^1, but nearly all the responding reflex is subsequent to the stimuli, and lasts for 1·75 sec.

Readiness for Integration.—Thus we see proximity of action, the policy of good neighbours, as it were, the blending which is integrated action of one kind of response with an allied kind of response into smooth movement from rest and back to rest again. But not only at these spinal levels is integrated action evident. Readiness, or fitness to be integrated, can be seen in still

more simplified preparations. In the skeletal muscle of the frog, Bronk found that the heat economy increased parallel with the mechanical tension, both reaching a maximum when the rate of stimulation was 4 a second, the muscle being at 0° C. (Fig. 5) (Bronk, 1930). Here we seem to have an example of mechanical integration of kinetic character, not just the static mechanical integration provided by the body's skeletal framework. In the cat, Cooper and Eccles found that the slow soleus muscle stimulated peripherally did not show much increase in tension after a stimulation rate as low as 10 a second had been reached,

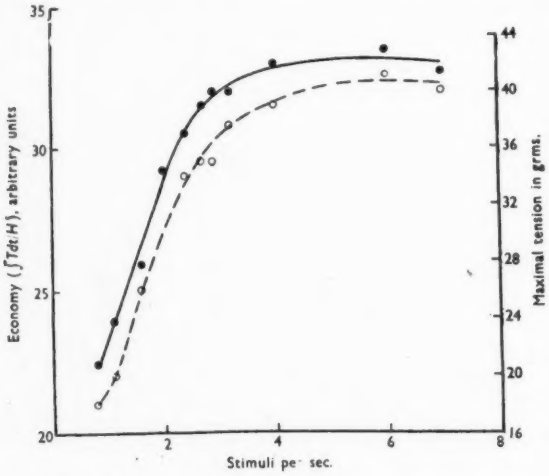

FIG. 5.—After Bronk, 1930. *J. Physiol.*, **69**, 311. Frog muscle at 0°. Upper curve, relation between economy and frequency of stimulation. Lower curve, maximum tension developed at various frequencies of stimulation. (By kind permission of the author, and the Editor of the *Journal of Physiology*.

whereas the rapid gastrocnemius muscle had to be stimulated at a rate of 35 a second before the rate of increase ceased to rise rapidly (Cooper and Eccles, 1930). These different rates for the two muscles are very suggestive of their being optimally attuned, as it were, to rates of natural stimulation appropriate for their functions, the slow soleus being concerned, as Denny-Brown showed, more with posture and the rapid gastrocnemius more with movement (Denny-Brown, 1929).

Readiness to co-operate and fitness to be integrated are again exemplified by observations of Gordon and Holbourn. They observed single reflex muscle units during slight progressive stretch. The first two reflex discharges are double discharges, so that by the summing of stimuli the increase in the muscle's mechanical tension is accelerated at the time when it is most needed by the organism (Gordon and Holbourn, 1948). Denny-Brown had earlier noted similar double discharges in reflex units at the inception of stretch (Denny-Brown, 1929).

Long Nerve Paths.—To integrate the behaviour of a long multi-cellular organism, long nerve paths seem to be an implicit necessity. Sherrington's oft-quoted words are profoundly true—the brain is the head ganglion of the distance receptors. The leading segments of the animal in its progress through its world are, as he said, exposed more to external influences than the hinder parts which follow. The leading segments meet more objects, receive more stimuli. The reactions of the distance receptors in the leading segments integrate the whole series of somatic segments. Conducting arcs pass from the cephalic receptors to the contractile masses of the body so that the distance receptors are the inaugurators of reaction. They integrate the individual not merely because of the wide ramifications of their arcs to effective organs, they integrate because of their great connexions in the high cerebral centres.

In this picture the pyramidal tract is an internuncial path. But there are many other internuncial paths, though of less notoriety. In the scratch reflex where, as we have seen, the cord has been isolated from all cephalic connexions, long intra-spinal paths with perikarya in the cord convey impulses from the receptive area on the skin of the back to the motoneurones which control the muscles of the hind limb. These are the long descending proprio-spinal fibres which lie in the lateral region of spinal white matter. For the scratch reflex of the spinal animal, Sherrington suggested the co-operation of at least three neurones, the efferent, the proprio-spinal, and the final common path to the muscle. In light of modern knowledge concerning the fleeting states of activity in single neurones, contrasted with the slow tempo of processes in the integrated scratch reflex, it is clear that many side-chains of interneurones must nowadays be postulated.

Other long intraspinal paths have recently been scrutinized with modern methods by Lloyd and McIntyre (1948). They have studied in the cat the time taken for a stimulus to a nerve of the fore limb to make its presence felt in motor neurones controlling the lower limb. The first sign of facilitation is detected after 8 milliseconds, and the effect on the lower limb's motoneurones is strongest at 15 milliseconds after the application of the stimulus. After 25 milliseconds the effect is over. The great pyramidal pathway has time relations which are

not much different. Stimulation of the pyramid at the cephalic end of the spinal cord is carried by fibres with a velocity of conduction in the cat of 60/65 milliseconds. Facilitation measured electrically of lower limb motoneurones begins 12 milliseconds after such stimulation, and the effect is gone after 35 milliseconds. Additional stimuli coming in singly after the first at 2·5-millisecond intervals do not alter the time-relations, but they increase the magnitude of the facilitating effect from the first stimulus. Three additional stimuli sent down the pyramidal tract, at 2·5-millisecond intervals, double the amount of facilitation, five nearly treble it (Lloyd, 1941). Increased inter-neurone speed, however, plays a part as well as increase in electrical activity and gives a clear picture of a double process in integration. Where the pyramidal fibres end at the dorsal group there is at first a latency of 4·5 milliseconds, and a latency of 3 milliseconds in the intermediate group of neurones, so that the total internuncial delay is 7·5 milliseconds. Subsequently, however, with repeated stimulation the total delay drops to be only 1 millisecond (Lloyd, 1941). " The more the better and faster " seems to be the integrated reply to repetitive stimuli.

It is well realized that we are only at the beginning of knowledge as to the functioning of that long big integrating pathway of pyramidal fibres. In 1909, only a few years after Sherrington's " Integrative Action " was published, Holmes and May wrote : " The cortical origin of the pyramidal fibres is not accurately known but the descriptions given of it are vague and discordant" (Holmes and May, 1909). Lassek's recent figures show that in man among the total count of 688,000 fibres in one pyramid only 30,000 fibres are of diameter as large as 9–22 μ ; 85 per cent. of pyramidal fibres are 1–4 μ in diameter, 61 per cent. are not myelinated (Lassek, 1942). What is the provenance, destination, and function of these numerous small fibres ? At least we can safeguard the future by refusing to assume that an anatomical entity of structure need imply a physiological unity of function. The small pyramidal fibres need not have and do not appear to have just the same function as the large.

Of long integrating paths outside the anatomical limits of the pyramid, knowledge begins to accumulate. An overall stimulation of the cerebral hemispheres and basal ganglia does appear to activate extra-pyramidal paths. Dr. Phillips and I have recently observed electrically induced epileptic fits in cats and made cinematograph film records (Liddell and Phillips, 1948). Before any section of the pyramidal path, the cerebral and sub-cerebral discharge registers its maximum effect in the body's musculature. After acute section of one pyramidal path, the limbs corresponding have much diminished movement. When both pyramids are acutely sectioned, muscle movement is almost absent, but nevertheless is not completely absent. From the *commotia cerebri* produced, excitation is travelling down the spinal cord by other routes. In preparations which have been made some months previously, the hind limb, with unilateral section, is still almost but not quite immobile, though the difference between the fore limbs is now less marked, owing presumably to the opening-up of other descending routes. When both pyramids have been sectioned some months previously, movement of muscles still persists. It is not until the cerebral and sub-cerebral nerve-masses are thrown out of action by deprivation of their blood supply (ligation of carotid and basilar arteries) that complete immobility of the body's skeletal musculature is achieved. Thus by this way of total stimulation combined with partial or total deprivation of pathways, we glimpse briefly the fields of control achieved by pyramidal and non-pyramidal intervention. Integration by long paths does not depend on only one anatomical path. To take but one example, the ever watchful vestibular apparatus is always at work in modifying the use of the limbs and the trunk so that the organism's total reactions resist gravity.

The Future

Full elucidation of the complex integration by long paths in the highest of all multicellular organisms, in man, is a problem for the future. No simple picture will be revealed eventually, but it seems safe to prophesy that the interdependence of function at every level of activity as well as fitness for the purpose can be expected as the prelude to integration throughout the nervous system. In Sherrington's brief phrase, " Each and every part of the animal is integrative."

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THE FATE OF AN INTRANEURAL INJECTION AS DEMONSTRATED BY THE USE OF RADIO-ACTIVE PHOSPHORUS

BY

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The history of the experimental investigation of such diseases as tetanus, rabies, and anterior poliomyelitis has so frequently involved the intraneural injection of the specific infective agent that some assessment of the potential spread of a small volume of indifferent material is long overdue.

The object of the present investigation was to determine the extent to which the intraneural injection of a crystalloid substance not exceeding 0·05 ml. in volume may enter the blood stream, the cerebrospinal fluid, and various regions of the nervous system. The choice of a radio-active tracer substance for this purpose was made not only because its detection is possible in very high dilution but because the curves of its concentration in both blood and cerebrospinal fluid can be plotted throughout the period of the experiment.

The chief consideration determining the selection of P 32 (as phosphoric acid) for this work was the fact that, provided the blood level does not exceed 750 to 800 counts/min./100 mg. (in the rabbit) there is no appreciable concentration of the tracer element in the spinal fluid (Table I). Further, within a survival period of two to two and a half hours there is no significant combination of the phosphorus with the lipoids and proteins of the nervous system as proved by the virtual absence of activity in the tissue residue after extraction with trichloracetic acid.

0·05 ml. was found to be the least volume which contained sufficient radio-active element to produce blood concentrations capable of estimation with no more than a probable error of 5 per cent. in a counting time of fifteen to twenty minutes per sample, a limitation imposed by the large number of samples taken in each experiment.

The injections were carried out at three different levels in the left sciatic nerve of the rabbit : (1) at the mid-femoral level (six experiments) ; (2) at the upper end of the popliteal fossa (four experiments) ; (3) at the level of the greater trochanter (six experiments).

A series of four control animals were given intravenous injections of 50 to 60 μc of P 32 and the curves of concentration in blood and cerebrospinal fluid plotted for a survival time of two hours. At the end of this period the activities of standard segments of the spinal cord and sciatic nerves were estimated as a basis for comparison with corresponding parts from the experimental animals (Table I).

Technique of Injection

Under nembutal anæsthesia the left sciatic nerve was exposed and complete hæmostasis secured before commencing the injection. The syringe used for injection was an all-glass tuberculin syringe into the nozzle of which the shaft of a No. 26 hypodermic needle was cemented. In this way "dead space" in the syringe was eliminated and a volume of 0·05 ml. could be delivered into a nerve without an accompanying air bubble. After the required volume of the indicator had been drawn up the needle tip was carefully dried.

The nerve was steadied by gripping its supporting connective tissue web just distal to the point selected for injection. The needle was then inserted slowly and always in a central direction at an angle of about 30° to the surface, until its point was thought to be well within the nerve substance. The injection itself took up to two minutes, depending on the degree of resistance encountered, while a small disc of filter paper applied to the point of entrance of the needle prevented any leak back along the needle track. At the conclusion of the injection the needle was left undisturbed for some thirty seconds while a fresh disc of filter paper was laid on the nerve at the entry point. The needle was now slowly withdrawn and two further paper discs successively applied, to be followed by a third which was left *in situ* and the wound closed over it.

It must be admitted that these precautions, while adequate to prevent any important modification of the subsequent blood concentration curves, were not so thorough as those of Abel and others(1935b) using tetanus toxin. Nevertheless the injections described above are far less likely to lead to leakage than the simpler procedures employed by the majority of workers with toxins and viruses. They have the further merit that there is minimal disturbance of the vascular connexions of the nerve.

The whole injection procedure was carried out under the binocular dissecting microscope and the features of each injection were recorded.

TABLE I

CONTROL EXPERIMENTS : SEGMENTS 1 TO 11 AS SHOWN IN FIG. 2

No.	Wt. Kg.	P32 μc	Max. blood level	Max. C.S.F. level	Right sciatic nerve				Left sciatic nerve				Spinal cord			Survival (minutes)
					1	2	3	4	5	6	7	8	9	10	11	
1	1·6	60	551	10·9	45·1	24·7	30·4	45·4	40·7	36·0	37·8	42·4	110·0	93·6	16·6	129
3	2·0	50	643	contam.	45·1	46·1	58·9	42·6	41·6	53·5	61·2	39·0	74·2	30·8	—	175
4	1·3	59	1042	Bkg.	43·4	47·9	38·3	26·6	46·3	43·8	31·3	28·3	56·2	18·1	10·5	150
6	1·8	50	730	7·1	52·0	53·3	52·7	53·9	66·8	65·7	55·4	43·8	67·8	38·9	15·7	138

Bkg. = Count virtually background.
contam. = C.S.F. specimen contaminated.

TABLE II

LOW SCIATIC INJECTIONS : LEVEL OF POPLITEAL FOSSA

No.	Wt. Kg.	P32 μc	Max. blood level	Max. C.S.F. level	Right sciatic nerve				Left sciatic nerve				Cord		Type of injection	Max. spread	Survival (minutes)
					1	2	3	4	5	6	7	8	9	10			
R.P. 10	2·0	55	162·0	21·2	66·9	125·5		52·7	∞		∞	342·5	150·4	57·4	High R. Mod. D	2/3rds of nerve	162
R.P. 11	2·2	55	112·6	10·2	27·9	78·0	20·1	26·3	∞	∞	65·9	27·5	40·5	26·6	Mod. R. D	Segment 6	142
R.P. 30	3·3	76	66·2	1485·0	27·5	24·6	21·1	61·2	∞	∞	∞	∞	∞	∞	Min. R. C	Basal ganglia	125
R.P. 31*	2·1	74	159·0	27·5	91·7	159·2	113·2	62·9	∞	∞	∞	∞	9400	280·0	Min. R. Slight D	Segment 10	122

R = Resistance to injection.
Min. R = Minimal resistance.
Mod. R = Moderate resistance.
C = Column of fluid seen to ascend nerve.
D = Dilatation of nerve at injection site.
Mod. D = Moderate dilatation.
∞ = Corrected count in excess of 15,000 counts/min./10 mg.

* Note R.P. 31. This injection had spread along the nerve to enter segment 9, without however causing any appreciable activity in the cerebrospinal fluid. In view of this and of the high blood level, this injection must be regarded as transitional between the two types.

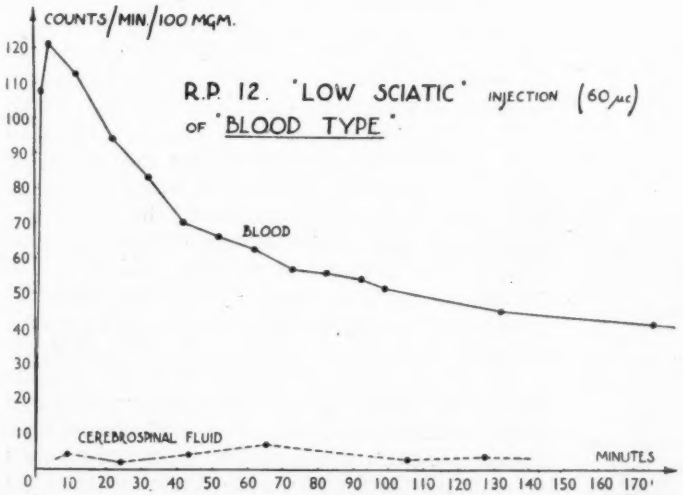

FIG. 1

FIG. 1.—Blood and cerebrospinal fluid curves in a typical "blood" type injection. The blood activity reaches a peak of 122 counts/min./100 mg. after five minutes, while the maximum cerebrospinal fluid activity is 9 counts/min./100 mg.

Collection and Estimation of Samples

Blood and Cerebrospinal Fluid.—Following the completion of the injection, samples of blood were taken from an ear vein, the first at one and a half to two minutes and subsequently at intervals of ten to fifteen minutes. Some four to seven specimens of cerebrospinal fluid (each about 0·1 ml.) were obtained at intervals during the experiment by cisternal puncture. The radio-active content of the samples which were absorbed on filter paper discs by the method of Reiss and others (1949) was estimated in a G.M. 4 " dry " counter with a Dynatron scaler.

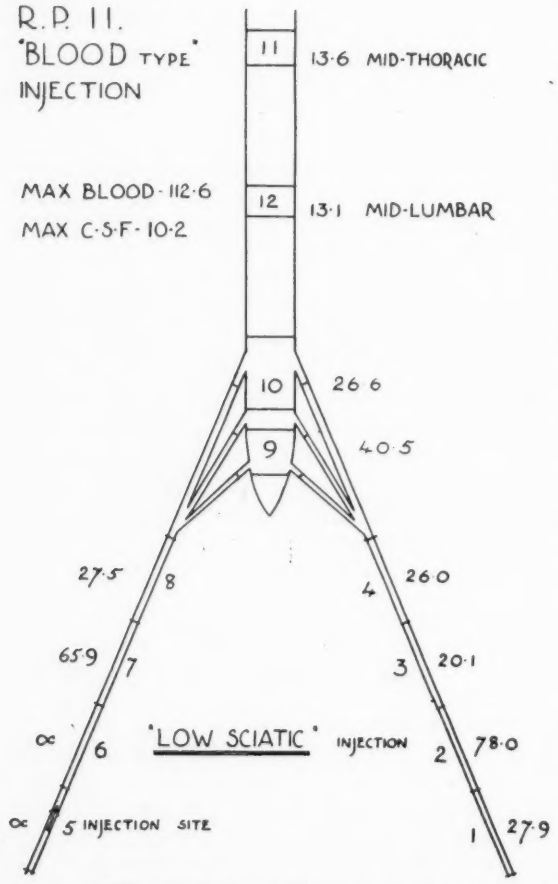

FIG. 2.—Diagram of the sciatic nerves and spinal cord divided into the standard segments, to illustrate a typical " blood " type injection with spread of the indicator confined to the two distal segments of the left sciatic nerve. The values of the spinal cord segments do not exceed those in the control experiments. Note the raised level of activity (78·0) in segment 2—the lowest contralateral effect in the series.

Sciatic Nerve and Spinal Cord.—After death the two sciatic nerves were fully exposed from popliteal fossa to sacrum and each was marked off into four equal segments with a pen compass dipped in red ink. Each segment was removed with minimal connective tissue, weighed on a torsion balance, and transferred to a clean homogenizing tube. The instruments used for the removal of the tissue samples were thoroughly cleansed after each removal. 2 to 3 ml. of 25 per cent. trichloracetic acid were added to each tube and the contents homogenized in accordance with the technique of Reiss and others (1949) for the determination of acid soluble phosphorous in the brain. The supernatant fluid obtained by centrifugation at 3,000 r.p.m. for three minutes was poured into an M.R.C. 1 " liquid " counter for estimation of radio-activity by the Dynatron counter as above.

Certain segments of the spinal cord were taken regularly from each member of the series and, like those of the sciatic nerve, numbered according to a standard plan (Fig. 2).

The spinal cord segments were dried with filter paper in order to remove cerebrospinal fluid before weighing. To standardize as far as possible the " personal equation," each worker performed the same duties throughout the series of experiments.

Calculation of Statistical Error.—Blood and cerebrospinal fluid samples were counted for not less than ten minutes unless highly active. Low activity fluids from cord or nerve samples were counted for not less than twenty-five minutes, while those of high activity were diluted sufficiently to render " paralysis time " corrections unnecessary. The background count of both " dry " and " liquid " counters was estimated for at least thirty minutes before the commencement of counting and for periods of one to two minutes between each sample.

From the count of a particular sample and the background count, the probable error on the corrected count (expressed as counts/min./100 mg.) was calculated by the method of Wilson Wright (1947).

Observations

1. Low Sciatic Injections (Table II)

Four injections were carried out at this level. Three of these had certain features in common and will be considered first. In each the resistance to be overcome increased as the injection proceeded, resulting in a variable degree of dilatation, seldom uniform but appearing as a localized bulging or an area of blistering confined to one section of the nerve circumference. In no case was a column of fluid seen to shoot up the nerve. In these three experiments the concentration of P 32 in the blood stream rose rapidly to between 112 and 162 counts/min./100 mg. (Fig. 1). In two cases the maximal blood activity was attained after twenty to twenty-two minutes, whilst in the third (R.P. 11) a particularly rapid absorption from the injection site produced the highest blood level a minute and a half after the injection. The cerebrospinal fluid in one case (R.P. 11) showed no more activity than was accountable for by the blood level, while in the other two (R.P. 10 and R.P. 31) the slightly higher

levels of 21·2 and 27·5 counts/min./100 mg. were found.

Assay of the sciatic nerves and spinal cord (Fig. 2) showed that there had been no direct spread of the indicator beyond the limits of the nerve itself (except R.P. 31 : see Table II), the concentrations in the spinal cord being attributable to the P 32 level in the general circulation (Table II).

An injection of this character resulting in a localized accumulation at the injection site or at most within the extent of the nerve and a rapid

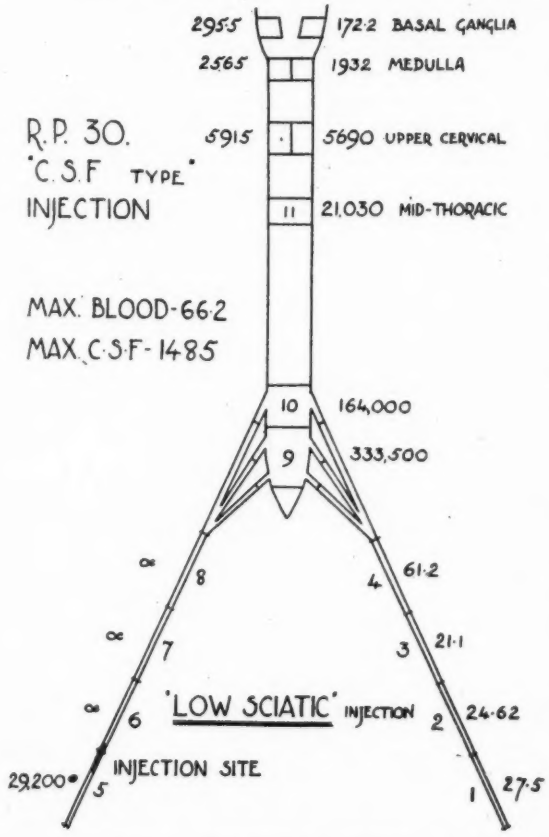

FIG. 3.—Diagram illustrating the spread of the tracer element in a " cord—cerebrospinal fluid " (C.S.F.) type injection. The indicator has passed along the sciatic nerve and the whole length of the spinal cord and brain stem to give substantial counts in the basal ganglia.

passage into the blood stream without direct extension to the spinal cord or cerebrospinal fluid may be termed a " *blood type* " of injection.

The nature and outcome of the fourth injection (R.P. 30) at this level were in marked contrast to the preceding three. Thus there was no appreciable resistance, an absence of dilatation of the nerve, and in addition a thin column of fluid was seen to pass up the nerve with great rapidity at the instant of applying minimal pressure to the syringe plunger. It was recorded that the resistance experienced in this particular injection was the least of the whole series. The maximal blood level attained at twenty-four minutes was only 66·2 counts/min./100 mg. while the cerebrospinal fluid exhibited an activity of 1,485 counts/min./100 mg. at the termination of the experiment.

Estimation of activity in the spinal cord samples showed that a remarkable spread of the tracer substance had occurred (Fig. 3), so that blocks of tissue taken to include the thalamus and corpus striatum gave counts considerably above their " control " level. Further the segments of upper cervical cord and upper medulla were divided in the median plane into right and left halves, and there was some indication that the injected material had ascended more extensively on the ipsilateral side.

In this one case, then, an injection associated with low resistance and the absence of dilatation of the nerve gave rise to a low level of blood activity, a highly active cerebrospinal fluid, and the spread of the tracer substance along the whole length of the spinal cord and brain stem An injection of this sort may be classed as of " *cord-cerebrospinal fluid type* " (abbreviation, C.S.F. type).

2. MID-FEMORAL INJECTIONS (TABLE III)

Six injections were carried out at the mid-femoral level. Of these, four were found to be of the " blood type " as defined above and two of " cord-cerebrospinal fluid type." In the former group, however, there was a certain spread of phosphorus within the nerve, so that in three cases (R.P. 8, 9, and 32) all nerve segments gave high counts. Spread into the nerve below the injection site took place in all four animals even though the needle had been directed proximally. The maximal blood levels lay between 73 and 274 counts/min./100 mg., while the maximum cerebrospinal fluid activity was 26·8 counts/min./100 mg.

In the two " cord-cerebrospinal fluid type " injections (Fig. 4), while the blood level did not rise beyond 40 and 81 counts/min./100 mg., the cerebrospinal fluid showed very considerable activity (4,078 and 2,565 counts/min./100 mg.), which could only be attributed to direct extension of the tracer from the injection site. Within the spinal cord the phosphoric acid had reached the mid-thoracic level in R.P. 13 and probably a considerably higher level in R.P. 14 in view of an activity of 6,100 counts/min./100 mg. at the thoracic level.

3. HIGH SCIATIC INJECTIONS (TABLE IV)

Of the six injections carried out at this level, three were effected with minimal or very slight

TABLE III

MID-FEMORAL INJECTIONS

No.	Wt. Kg.	P32 μc	Max. blood level	Max. C.S.F. level	Right sciatic nerve				Left sciatic nerve				Cord		Type of injection	Max. spread	Survival (minutes)
					1	2	3	4	5	6	7	8	9	10			
R.P. 8	2·5	60	274·2	16·2	47·8		60·7	39·8	∞		∞	13,640	99·7	20·7	Mod. R. D	Most of nerve	155
R.P. 9	2·2	55	73·2	26·8	238·8		23·8	22·7	∞		∞	∞	10·3	6·1	Mod. R. D	Whole nerve	155
R.P. 12	1·6	60	120·8	7·2	114·5	75·0	70·6	51·7	∞	∞	3490	43·6	42·0	21·1	Slight R. Mod. D	Segment 7	180
R.P. 32	2·9	74	159·0	Bkg.	91·7	159·3	113·2	62·9	∞	∞	∞	∞	86·2	37·2	Min. R. C	Segment 8	130
R.P. 13	4·5	65	81·6	4078	242·3	129·2	74·2	90·1	∞	∞	∞	∞	∞	1413	Min. R. C	Mid-thoracic	145
R.P. 14	2·3	50	40·3	2565	27·7	22·6	19·4	20·9	∞	∞	∞	∞	∞	∞	Min. R. C	Above mid-thoracic	130

Symbols as in Table II.

TABLE IV

HIGH SCIATIC INJECTIONS

No.	Wt. Kg.	P32 μc	Max. blood level	Max. C.S.F. level	Right sciatic nerve				Left sciatic nerve				Cord		Type of injection	Max. spread	Survival (minutes)
					1	2	3	4	5	6	7	8	9	10			
R.P. 24	1·8	50	142·0	6·9	68·6	56·9	94·2	68·1	269·6	8990	∞	∞	5400	196·0	Min. R.	Segment 10	133
R.P. 27	2·2	60	192·3	39·7	100·8	54·4	55·2	132·0	164·0	7675	∞	∞	∞	∞	Min. R. C	Basal ganglia	124
R.P. 28	2·2	65	86·0	32·6	88·9	71·4	37·8	68·9	78·8	3415	∞	∞	108·8	69·6	Mod. R. Slight D	Segment 9	9
R.P. 25	1·6	50	148·4	5·7	57·9	54·6	48·5	55·1	689·0	7200	∞	∞	234·6	56·2	Mod. R. D	Segment 9	130
R.P. 26	2·0	60	95·7	76·9	153·7	72·0	43·2	24·0	109·0	∞	∞	∞	61·1	9·9	R. D.	Segment 8	125
R.P. 29	2·9	55	45·2	17·5	234·5	77·8	56·6	32·3	59·3	2230	∞	∞	67·3	60·0	R. D.	Segment 8	135

Symbols as in Table II.

resistance and an absence of distention of the nerve. They resulted in a considerable spread of the indicator, in one case (R.P. 27) as far as the basal ganglia, while the least spread (R.P. 28) was as far as spinal cord segment 9. From the behaviour of injections at lower levels in the nerve it might have been expected that a high degree of activity of the cerebrospinal fluid would be associated with this widespread penetration of the spinal cord, yet it was in fact noted that *in none of these three animals did the cerebrospinal fluid activity exceed* 40 *counts/min./*100 *mg.* (R.P. 27). Again the blood activity, which it was anticipated would be low, attained a level of 192·3 counts/min./100 mg. in R.P. 27.

Injections of this type featuring direct spread to the cord but not to the cerebrospinal fluid may be classed as of "*cord type*" (Fig. 5). The absence of the tracer substance from the cerebrospinal fluid in the face of a high concentration in the spinal cord is remarkable, particularly after two hours, during which time diffusion from cord to fluid might have been expected to take place.

The survival period of one of these animals was

only nine minutes (R.P. 28), its death occurring at the first cisternal puncture. It is of interest that within this space of time the tracer substance had passed up to the level of the upper sciatic entry segment (10) to produce a count of 108·8 counts/min./100 mg. In view of the high activity (∞) of segment 8 of the sciatic nerve, and the low maximum blood level (86 counts/min./100 mg. after one minute) and a cerebrospinal fluid count of 32·6 counts/min./100 mg., it appeared that the activity of segment 10 must be attributed to spread of the indicator from the sciatic nerve (c.f. control range (10) 18·1—93·6 : with blood range 551–1,042 counts/min./100 mg.). This fact, together with the low resistance encountered during the injection, justified the inclusion of this experiment in the " spinal cord " group.

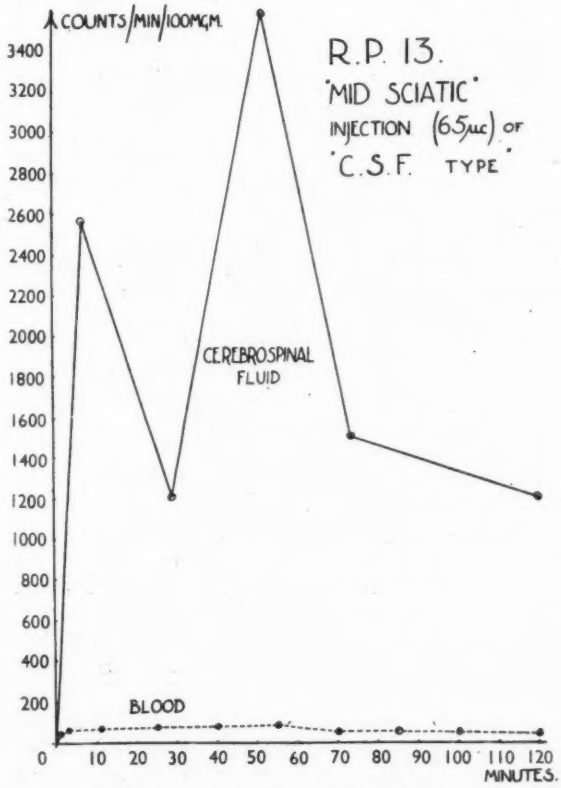

FIG. 4.—Blood and cerebrospinal fluid curves in a typical " cord cerebrospinal fluid " (C.S.F.) type of injection. The blood activity does not exceed 82 counts/min./100 mg. while that of the cerebrospinal fluid reaches 4,078 counts/min./100 mg.

The remaining three injections were of " blood " type, the maximal blood concentrations ranging from 45 to 148 counts/min./100 mg., the former rather low blood level probably being due in part to the injection of only 55 μ c into a large animal (2·9 kg.). The cerebrospinal fluid activity in this group was rather higher than in the " blood " type injections at the mid-femoral and low sciatic levels, reaching 76·9 counts/min./100 mg. in R.P. 26 after forty minutes. In one case (R.P. 25) a slight direct

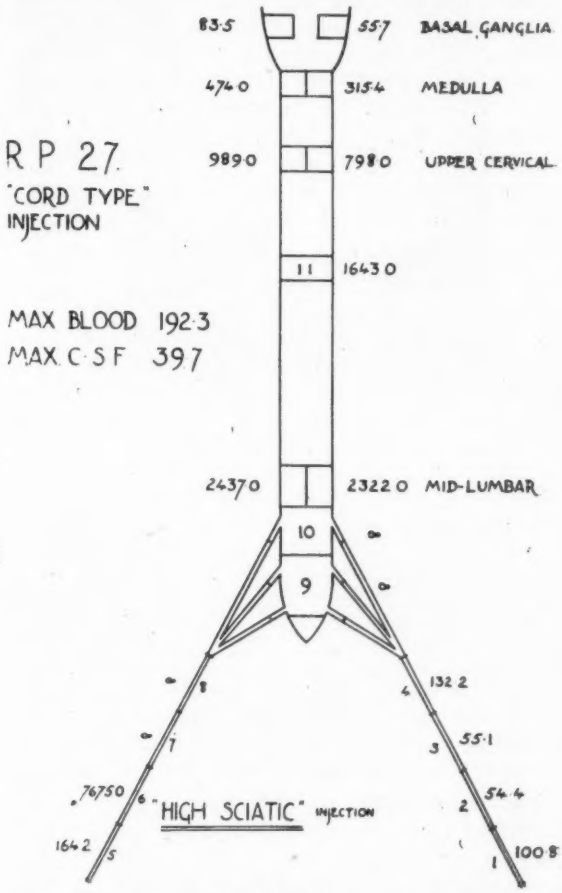

FIG. 5.—Diagram illustrating spread of the tracer element in a " high sciatic " injection of " cord " type. The blood level is high (192·3), while that of the C.S.F. (39·7) is remarkably small compared with the highly active cord throughout its length. Note the raised level of activity of segments L and 4. The injection site is at the lower limit of segment 8.

extension to the spinal cord took place (234·6 counts/min./100 mg. in segment 9), suggesting that this particular injection is intermediate between " cord " and " blood " types.

Changes in the Opposite Sciatic Nerve.—Interesting and unexpected findings were noted in the uninjected sciatic nerve which was divided into the usual four segments for estimation of radio-active content. In thirteen of the sixteen experiments,

the activity of one or more segments of the contralateral nerve was considerably higher than the average control value. Further, in eight of the thirteen animals showing the effect, the elevated activity of the opposite nerve segments showed a rough correspondence to the site of the intraneural injection, while in the remaining five cases the effect occurred in one or both of the two distal segments. Tables II, III, and IV show the incidence and localization of the effect in the three groups of injections. It is evident that the contralateral effect is less marked in the " low sciatic " injections than in the " mid " and " high sciatic " types, in which it was noted in four out of six and five out of six cases respectively.

Anatomical Localization of the Injection Mass.—The resolution of intraneural injections into two main groups on the basis of the immediate behaviour of the injection mass has prompted a further enquiry into the anatomical localization of the needle point and of the indicator material in the two types. In order to obtain precise histological information a suspension of indian ink was employed, bearing in mind the much greater resistance to flow of such a suspension compared with the crystalloid radio-active material.

A number of injections of filtered indian ink of particle size 0·5–1·5 μ were made into the sciatic nerves of anæsthetized rabbits at the mid-femoral level. A volume of approximately 0·1 ml. of ink was introduced through the same type of needle as was employed in the previous tracer experiments. After a survival of ten minutes the animals were killed and the sciatic nerves removed, examined, fixed in formalin and embedded in celloidin. Transverse sections of the nerves were cut at 12 μ and stained with alum carmine.

Gross Appearances.—It was again noted that the injections fell into two main groups whose local characteristics were closely similar to those of the tracer indicator. In the first type, the injection encountered little resistance and a sharply defined black column could be seen to run up the undistended nerve for at least 1·5 cm. In several instances a similar column of ink was seen to move in a centrifugal direction for a somewhat lesser distance, recalling the high activity of segments distal to the injection site in certain of the tracer experiments. From the close similarity between the features of these ink injections and those of radio-active phosphorus of " cord-cerebrospinal fluid " type, it was considered that the low- and high-power appearances so obtained could justifiably be used to elucidate the behaviour of the indicator in this group of tracer injections.

Low-power examination of the nerve sectioned transversely near the apex of the ascending column of ink showed clearly (Fig. 6A) that the ink was confined to the centre of one of two large fasciculi. Viewed longitudinally in the intact specimen the ink column appeared to lie deeply in the nerve substance, the exterior of the nerve being unstained even at the injection site.

In the second type there was considerable resistance to injection, and this was associated with localized distention of the nerve. Beyond the limits of the local bleb an irregular band of ink extended for only a few millimetres and the exterior of the nerve appeared black. These features closely resemble those of the " blood " type phosphorous injections, for which it was felt they could provide an anatomical basis.

A transverse section made through the injection site in the fixed specimen allowed a little free ink to escape and the binocular dissecting microscope revealed the appearances shown in Fig. 6B. It can be seen that the ink has stained the exterior of the nerve but also forms a thin black line separated from the nerve's circumference by the thickness of the perineurium. It seems probable, then, that the injection has created a restricted sub-perineural space along which no considerable penetration is possible.

Microscopic Examination.—In those nerves where the injected ink had spread freely with little resistance it was distributed throughout the substance of the fasciculus, producing a characteristic " wire-netting" picture due to the presence of particles between the individual nerve fibres (Fig 6C). This section, taken near the injection site, shows that some ink had penetrated into the " sub-perineural space." Little if any ink is to be seen in the connective tissue of the nerve trunk.

The injections resulting in bleb formation and little spread along the nerve are represented by Fig. 6D, which is a section taken at the injection site. The ink lies largely in and below the perineurium, while a relatively small amount lies in the inter-fibre spaces, along which low-power observations have shown that progress is strictly limited.

It may be concluded from the above that the " cord-cerebrospinal fluid " type of injection takes place when the needle point lies at or near the centre of a nerve fasciculus, from which the injection mass moves freely in the inter-fibre spaces—the paths of least resistance within the nerve. On the other hand the " blood " type of injection occurs when the needle point lies within or just below the perineurium. The injected material then creates an artificial sub-perineural space, but only when considerable resistance has been overcome. A variable degree of penetration of the fasciculi also

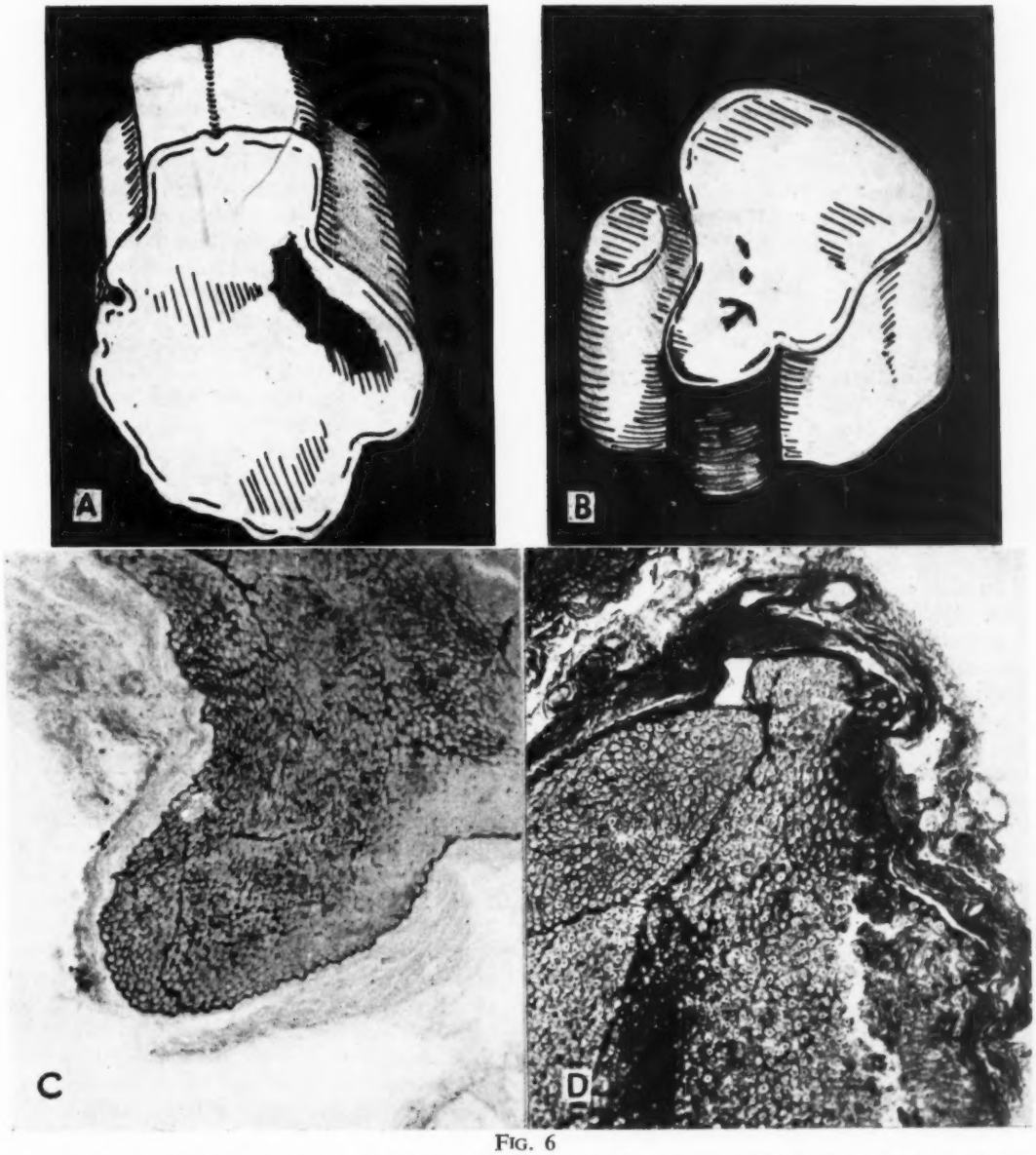

FIG. 6

A. Sketch of cut end of nerve injected with indian ink (×25). "C.S.F." type of injection. Section taken near apex of ascending ink column, which is seen to lie within the substance of a fasciculus and separated from the perineurium by unstained fibres. The exterior of the nerve is unstained.

B. Sketch of cut end of nerve injected with indian ink (×25). "Blood" type of injection. Section taken at injection site showing staining of the exterior of the nerve, the presence of ink in a sub-perineural depot and a small quantity within a fasciculus due to penetration to this situation at a slightly different level.

C. Transverse section of a nerve injected with indian ink (×75). "C.S.F." type of injection. Section taken at base of ascending ink column. Ink particles are seen to lie within the fasciculus between individual nerve fibres to present a typical "wire-netting" appearance. A thin film of ink lies under the perineurium at this level but it extends for only a few millimetres.

D. Transverse section of a nerve injected with indian ink (×75). "Blood" type of injection. Section taken close to injection site. Considerable ink is seen to lie within the artificial sub-perineural space which is confined to a part of the nerve circumference. At this level ink particles have penetrated a fasciculus to give the "wire-netting" appearance but have not been able to ascend more than a few millimetres.

takes place, but is not sufficient to spread any large distance along the nerve.

It must be admitted that these ink injections, carried out as they were at the mid-femoral level, invariably failed to produce evidence of ink in the sub-arachnoid after an interval of several hours. Our experience with soluble dyes has been quite different and has provided confirmation of the claim made by Horster and Whitman (1931–2) that high intra-sciatic injections of dye not in excess of 0·1 may easily enter the cerebrospinal fluid as well as the spinal cord.

Discussion

It is a legitimate criticism that all too often the experimental production of a disease by intraneural injection of toxin or virus has been regarded as evidence of the passage of that agent along neural pathways by virtue of forces inherent in the nerve itself. Further, the vascular components of the nerve, both blood and lymphatic, have, with certain notable exceptions, received inadequate consideration in the interpretation of such experimental results. It is therefore desirable before making reference to the relevant experimental work on tetanus and anterior poliomyelitis to review certain of the anatomical features of a typical peripheral nerve.

The sole neural element establishing an unbroken connexion between the periphery and the central nervous system is the axis cylinder, the structure currently believed to provide the pathway of transport for tetanus toxin and the virus of rabies, poliomyelitis, and certain other virus diseases. In this connexion it must be admitted that evidence is lacking of any centripetal flow within the axoplasm capable of conveying an infective agent from periphery to centre within the incubation period of the disease. On the contrary it has been suggested by Young (1945) that there is in fact a slow centrifugal streaming of the axoplasm away from the parent cell body.

However, the possibility of a surface streaming of virus particles is provided by the experiments of McFarlane (1940), in which buffered suspensions of vaccinia virus were placed in the U tube of the Tiselius apparatus. It was observed that the particles exhibited an endosmotic streaming along the centre of the tube, associated with a movement of the buffer in the opposite direction. McFarlane has suggested (personal communication) that such a mechanism might explain the movement of virus along a sectioned peripheral nerve whose central end is dipped in a pool of virus, as in the experiments of Bodian and Howe (1940, 1941 a and b). The necessary physical conditions could exist, not inside the axis cylinder, but within the capillary layer of fluid occupying the intervals between the individual nerve fibres. It is evident that such a film must lie outside the myelin sheaths, as no spaces are known to exist between the axis cylinder and the myelin sheath nor between the myelin sheath and the neurilemma (De Renyi, 1932).

The sleeve-like outer coat of the nerve, the perineurium, is separated from the contained fasciculi by the no more than potential sub-perineural space. This latter is often referred to as a true space from the appearances seen in paraffin sections, where shrinkage is largely responsible for its production, whereas celloidin sections fail to reveal any interval in this situation. The existence of connective tissue septa between perineurium and endoneurium represents a barrier to any physiological flow in either a centrifugal or a centripetal direction. Nevertheless the possibility remains that material introduced by direct injection may find the sub-perineural space to be one of the pathways of least resistance within the nerve and therefore analogous to the inter-muscular fascial planes as a potential avenue of fluid movement (compare the fascial spaces in the palm).

That the endoneural spaces do not establish any physiological communication with the subarachnoid space has been established by Weed (1914), Iwanow (1927), Elman (1923), and Brierley and Field (1948). Thus neither crystalloid nor particulate substances when introduced into the cerebrospinal fluid under physiological pressure conditions will pass farther along a spinal nerve than the proximal pole of its dorsal root ganglion. On the other hand Sullivan and Mortensen (1934) showed that in the rabbit coloured brominol oil introduced into the cisterna magna after removal of a corresponding volume of cerebrospinal fluid could be seen to pass some distance along the major peripheral nerves, both by *x*-ray examination and by dissection. Some twelve to twenty hours were required to obtain this effect, and at necropsy the oil in the sciatic nerve at the level of the greater trochanter was seen to lie both within and around the fasciculi. Deposits of the coloured oil also occurred free in the tissues surrounding the nerve. Such findings are in sharp contrast to those obtained with both Weed's crystalloid mixture and with indian ink suspensions, and suggest that an oily medium is better able to pass through the cul-de-sac of the sub-arachnoid space around the nerve roots, but once again they emphasize the need for a precise study of the anatomy and properties of the various membranes in this situation. Under the artificial conditions of intraneural injection, Key and Retzius (1875) were the first to show that an injection mass could be

made to pass from a peripheral nerve into both the cerebrospinal fluid and the substance of the spinal cord. This finding was again noted by Horster and Whitman (1931–2), and has been confirmed in the present investigation.

The blood supply of the sciatic nerve of the rabbit has been described in detail by Adams (1943), who pointed out that a nerve is never supplied by a single artery but by a number of vessels, each of which divides into ascending and descending branches before penetrating the perineurium to enter the inter-fascicular connective tissue. Here a rectangular network of branches is formed from which the capillary plexuses are derived, and these alone extend into the endoneurium. The vessels of a nerve are not end arteries but form a longitudinal arterial network. It can thus be seen that a nerve is a richly vascular structure affording a considerable capillary bed from which injected substances may be absorbed.

Defrise (1930) has elucidated many of the problems relating to the lymphatic drainage of nerves, and in addition to a rich plexus lying on the epineurium has described communications between this plexus and lymphatics lying within the nerve substance in the inter-fascicular planes. The existence of such intraneural lymphatics has always been denied, and this finding of Defrise has not been confirmed by Zhdanov (1931)

Any consideration of the ultimate fate of a substance injected into a nerve must take into account the anatomical factors enumerated above, and it is clear that a nerve cannot be regarded as a route leading solely to the central nervous system, but rather as a tubular system of neural units containing potential spaces and affording opportunities for absorption into the general blood vascular and lymphatic systems closely similar to those in any other tissue of the body.

The well-known work of Key and Retzius (1875) provided the first evidence that intraneural injections of dyes could reach the subarachnoid space of the spinal cord and brain, and these workers drew attention to the lack of uniformity of spread in any group of injections. Thus in some instances Key and Retzius noted the " oft wunderbare Leichtigheit " with which intraneural injections of dyes could be carried out in the perineural lymph sheaths, that is, in the endoneural spaces, while in other cases there was little appreciable spread of the injection mass. Comparable observations were made by Horster and Whitman (1931–2) when carrying out intraneural injections of trypan blue. It was recorded that in those animals (rabbits) where staining of the spinal cord or of the cerebrospinal fluid was obtained, the injection was made with the greatest of ease, and the impression was gained that the injection was passing into natural preformed pathways in which only a minimal pressure existed. In certain cases, however, the injection produced a local bleb, the dye only spreading up and down for a short distance without reaching the cord.

The " cerebrospinal fluid " types of injection described in the present series of experiments may be regarded as corresponding to those of Key and Retzius and of Horster and Whitman, in which the dye stuff could ultimately be detected in the spinal fluid. The " blood type " of injection associated with resistance to injection and distention of the nerve probably corresponds to those injections of the earlier workers in which there was bleb formation together with minimal spread of the dye. Clearly, then, the position of the needle point in the nerve is an important factor determining the spread of an injection and is largely a fortuitous circumstance. Attempts to produce at will one or other type of injection are in most cases unsuccessful.

A further and obvious factor is the volume of the injection employed and here the present investigation has shown that so small a volume as 0·05 ml. of a crystalloid material may on occasion run from the lower part of the sciatic nerve up to the basal ganglia under even minimal injection pressure. It is probable, therefore, that injection volumes used by many workers may spread widely in the nervous system and produce relatively high concentrations in even remote parts. Thus Yuien (1928), injecting 0·5 ml. of trypan blue into the sciatic nerve of a rabbit at the mid-femoral level, observed the passage of the dye along the ventral roots of the nerve into the spinal cord and cerebrospinal fluid. The conclusion reached from these and similar experiments with Weed's solution was that the flow of nerve lymph was centripetal in motor nerves and centrifugal in sensory nerves, a conclusion completely without justification in view of the large quantity of dye injected. This objection applies with even greater force to the experiments of Yuien and Sato (1929), who injected the heroic volume of 15 ml. of " Dekalin " in a central direction into a peripheral nerve of a rabbit. The injection was carried out " slowly under a little pressure," and the stain was observed to travel largely in the subperineural space to the subarachnoid space. This was taken to demonstrate that dyes made up in a non-aqueous medium could travel with greater rapidity than those dissolved in water.

Turning now to those experiments in which infective agents were introduced into the body by intraneural injection, the literature of the experimental investigation of tetanus reveals frequent

inattention to the complex nature of a peripheral nerve and the importance of the factors of injection volume, injection pressure, and position of the needle point.

Of the many workers who have contributed to the development of the theory of axonal transmission of the toxin, Marie and Morax (1902) are well known. A single dose of 3 g. of tetanus toxin (equivalent to about 1,000 lethal doses) was injected into the gastrocnemius muscle of a pony which died less than three days later. The first development of tetanic symptoms in the injected limb was adduced as evidence for the passage of the toxin along the peripheral nerves to the related spinal cord segments. Nevertheless these workers admitted that in a given weight of the sciatic nerve the content of toxin is exactly what calculation showed should be present if the total dose were equally distributed in every organ and tissue.

Meyer and Ransom in the same year, from a series of experiments in which the toxin was injected intraneurally, concluded that its absorption from the nerve took place via the neural lymphatics. The latter delivered the toxin into the general blood stream, from which it could only gain access to the central nervous system along motor nerves from their endings in muscle.

Further intraneural injections of tetanus toxin were carried out by Horster and Whitman (1931–2) employing an injection volume of 0·04 to 0·1 ml. These experiments indicate clearly the importance of the factors of injection pressure and the position of the needle point, and closely parallel the earlier investigation by the same workers in which trypan blue in similar volumes was injected into the sciatic nerve. Thus in five out of fifteen experiments the toxin could be identified in cerebrospinal fluid (cisternal puncture) very soon after the original injection. In the remaining cases the toxin never appeared in the liquor and was found to have passed only a short distance up and down the nerve. Abel's (1935) criticism of these experiments is that " . . . when Horster and Whitman did not succeed in driving the toxin into the lumbar cerebrospinal fluid at once by syringe pressure, the cisternal fluid never contained any of it later, even when the authors waited almost three days for signs of its appearance" (p. 105) ; and further, when the toxin fails to spread far from the injection site, " . . . it cannot be carried into the central nervous system by forces naturally inherent in the nerve or by its lymphatics."

In a discussion of the intraneural channels available for fluid movement Abel draws attention to the lack of evidence in support of any centripetal flow within the axis cylinder, while in relation to the question of fluid flow within the tissue spaces (" lymphraume ") Abel writes, " The tissue pressure at peripheral points is not of sufficient magnitude to move solutions through such narrow spaces, frequently interrupted as they are by tissue barriers. These minute spaces are energized by molecular forces only (surface energy and diffusion) and it remains to be proved that such forces can compass the astonishing feat of transporting a poison for long distances, as in the sciatic nerve of a horse, and through intervening cell barriers to the central nervous system, in any period of time that could ever come into consideration under experimental conditions or in the naturally occurring disease, tetanus" (p. 107).

In order further to discredit the concept of neural transport, Abel and others (1935) carried out a series of intraneural injections of tetanus toxin using a volume of only 0·025 to 0·083 ml. and with most stringent precautions to prevent leakage. It was recorded that in no case were symptoms of central tetanus seen to occur, the animals remaining normal for twenty-four days except for a slight local rigidity which was attributed to undetected leakage of toxin. In the absence of any movement of the toxin along the nerve to the central nervous system no symptoms were produced, whereas a similar dose injected intramuscularly produced typical local tetanus, so that, " We must conclude that intraneurally injected toxin, when its local escape has been avoided, is conveyed in its entirety away from the nerves by their lymphatic trunks to the venous system" (p. 320). The failure of the dose of toxin used, to produce symptoms on entry into the blood stream was considered to be due to its relatively low rate of absorption : " . . . an intraneural injection of toxin is exactly equivalent to a slow intravenous injection of an equal dose" (p. 332).

The scope of Abel's work is too large for review here, but a series of convincing arguments are put forward to support the view that in tetanus the muscular rigidity is due to the direct local action of the toxin on the normally innervated muscle and that the spread of the disease to the " general " form is explicable solely by dissemination of the toxin in the blood stream. Once again, " The history of science bears testimony to the fact that it is not easy to dislodge from the mind a theory that has long been whole-heartedly accepted." (Abel and others, 1938, p. 399.)

Any review of the origin of the current theory of axonal progression of the virus of anterior poliomyelitis would be out of place in this communication, and attention must be confined to an examination of certain of those experiments involving intraneural injection of the virus, the results of which have been adduced as support of this theory. In

this connexion the well-known experiments of Hurst (1930) must be re-considered in the light of the observations here presented. The intra-sciatic injection of 0·5 ml. of a virus suspension, together with deliberate trauma of the nerve by the injecting needle, was found to be a certain method of producing the disease in the monkey. The progress of the virus was found to be from the lumbar cord to the opposite motor cortex, the cervical region and the ipsilateral cortex giving evidence of virus at a later date. It was considered that this behaviour would be expected were the pyramidal fibres the transmitting structures. It is now clear that the passage of the injection mass to the lumbar region is a highly probable consequence of so large an injection, carried out as it was in the upper half of the sciatic nerve. Further, the deliberate trauma occasioned by moving the needle point up and down within the nerve almost certainly ensures that the subsequent injection shall be of the "cord-cerebrospinal fluid" or "cord" type rather than the localized "blood type," a finding recorded on several occasions when trauma to the nerve with the needle point was deliberately associated with an injection of radio-active phosphorus.

The proved spread of the tracer injection along the whole length of the spinal cord and brain stem to the basal ganglia at once raises the question whether such a tracer injection in a monkey with well-developed crossed pyramidal tracts would not in fact tend to follow the endoneural spaces of these bundles to give higher levels of activity in the opposite hemisphere. If this were so, the initial distribution of virus throughout the length of the central nervous system may well be explicable solely as the result of injection pressure, while its subsequent concentration in the brain stem and spinal cord enlargements and in the motor cortex may be related to the particular affinities for virus of the cells of these regions.

The distribution throughout the neuraxis of a proportion of intra-sciatic injections of 0·05 ml. of tracer substance suggests that extra-axonal pathways are concerned, and of these the endoneural spaces of peripheral and central nervous system are most probable. This is supported by the peri-axonal "wire-netting" appearance of sections of nerve injected with indian ink and also by the rapidity of movement of the radio-active indicator. Thus a distance of 35 to 40 cm. is traversed in a period of 120 to 140 minutes, a velocity far greater than has ever been suggested for intra-axonal progression. Further information concerning the actual velocity of the tracer movement is obviously desirable and could be obtained from similar injections carried out with shorter survival periods. It is unfortunate that facilities have not been available for the completion of such experiments which alone can demonstrate the true speed of crystalloid spread in the nervous system.

When a comparison is made between an intraneural injection of virus and one of a crystalloid, allowance must of course be made for the heterogeneous particulate nature of the former, which could impair its ability to traverse capillary spaces and so reduce the speed and extent of its spread. However in spite of this, endoneural spaces must still afford the main avenue for rapid progression of the virus suspension consequent upon the act of injection. Such a mechanism of distribution is in fact that described by Römer (1913), who, in relation to intra-cerebral injections of virus, stated that, "Should these observations be confirmed they would seem to indicate that the active agent spreads along the neurone, or at least, spreads more quickly in this direction than in any other. It is to be supposed that in doing this it passes along the lymph channels accompanying the neurone, although this would presuppose a considerable degree of isolation of these channels" (p. 99).

In this connexion it is interesting to note that O'Leary and others (1932) observed that the functional activity of nerve fibres, as measured by the cathode ray oscillographic technique, remains normal until demonstrable changes occur in the nerve cell. They therefore suggest that the virus may travel between the nerve fibres, in which case Hurst's (1930) results after sciatic inoculation may be attributable to the passage of virus along the path of least resistance between the pyramidal fibres, rather than within them. Further, Howe and Bodian (1942), in their discussion of the mechanism of intraneural virus spread, state: "... in fact it is possible that instead of being adsorbed on the surfaces (of the axones), virus particles may move along interfaces in a gel at velocities greater than is possible by simple diffusion" (p. 24). If this suggestion and that of McFarlane (*vide supra*) are substantiated, we may well witness the abandonment of the original hypotheses of Di Vestea and Zagari (1887, 1889) in favour of a mechanism which differs in no important respect from that of Römer whose "perineural lymph spaces" are the capillary intervals whose physico-chemical properties are now under discussion.

The considerable blood absorption from a proportion of intraneural injections raises the question whether similar absorption may take place from the central end of a divided nerve when dipped in the tracer indicator. The problem is important in view of the technique adopted by Bodian and Howe

(1940), in which the sectioned monkey sciatic nerve was dipped in a pool of poliomyelitis virus for ten minutes. This was found to be a very reliable method of producing the disease. The possibility of absorption into the blood was not considered by these authors, for whom the pathway of virus to the central nervous system lies solely within the nerve. However, the work of Lennette and Hudson (1936) and German and Trask (1938) suggests that modifications in the blood-brain barrier may permit circulating virus to invade the central nervous system and indicates that spread by the blood is a problem that even now merits further enquiry.

The central end of the cleanly sectioned rabbit sciatic nerve was inserted in one limb of a U tube containing radio-active phosphoric acid as described by Bodian and Howe (1940).

Preliminary results have shown that there is in fact appreciable absorption into the blood to produce activities of 55 to 60 counts/min./100 mg.; after fifteen minutes' contact with the indicator. Caution must, however, be exercised in carrying over these results obtained with a crystalloid material to the problem of virus absorption in similar experiments.

Significance of the Contralateral Effect.—The mechanism responsible for the heightened activity in the contralateral nerve cannot be elucidated in full from the present experiments, designed as they were to solve a different problem. The most that can be said is that a particular segment of nerve contains more radio-active phosphorus than would be expected from the maximum blood level of the experiment. It is clear that the source of this phosphorus can only be the blood stream, as the possibility of streaming from the injected nerve or from the spinal cord is excluded by the occurrence of normal counts in the segments between the cord and the region of increased activity. Presumably there is some change in the peripheral blood-nerve relationship associated with either an increased vascular permeability or an increased phosphorus interchange between blood and nerve.

A survey of the features of all the injections concerned leads to the suggestion that trauma may be the most important single factor in the production of the effect. It is noteworthy that the contralateral activity was least in an injection that was recorded as " the easiest of the whole series " and most in an injection where trauma with the needle point was deliberately inflicted. If this should prove to be the case, the mechanism involved is most likely to be nervous and of reflex type.

A contralateral change of this type appears to resemble the observations of Barnes and Trueta (1942). These workers noted that after the application of a tourniquet to one limb of a rabbit " in some of the animals there was . . . a well-marked spasm of the femoral artery of the *uninjured* limb, the spasm beginning at a level corresponding approximately with the site of the tourniquet on the other limb."

Summary

1. A technique for introducing 0·05 ml. of radio-active phosphorus (as phosphoric acid) into the sciatic nerve of the rabbit is described.

2. Of the sixteen injections performed, four were at the apex of the popliteal fossa, six at the mid-femoral level, and six just above the greater trochanter.

3. The injections fell into two groups according to their immediate local features and to the subsequent distribution of the indicator in blood, cerebro-spinal fluid, and the nervous system. The outcome of any one injection was purely fortuitous.

4. The following features distinguished a " cord-cerebrospinal fluid " type of injection :

i. Minimal resistance to injection.
ii. Absence of dilatation of the nerve.
iii. A column of fluid moving rapidly in a central direction.
iv. Spread of the indicator throughout the nerve.
v. Spread of the indicator into the spinal cord.
vi. Entry of the indicator into the cerebrospinal fluid.
vii. Relatively little absorption into the blood stream.

5. The following features distinguished a " blood " type of injection :

i. Considerable resistance to injection.
ii. Variable dilatation of the nerve.
iii. Absence of an ascending fluid column.
iv. Limited spread of the indicator within the nerve.
v. No spread of the indicator into the spinal cord.
vi. No entry of the indicator into the cerebrospinal fluid.
vii. Considerable absorption into the blood stream.

6. " High sciatic " injections resembled the " cord-cerebrospinal fluid " injections except that there was no appreciable entry of the indicator into the cerebrospinal fluid, while blood activity was relatively high. The term " cord " type was applied to these injections.

7. Changes were reported in the opposite sciatic nerve in which the activity of one or more segments was considerably higher than the average control values.

8. Indian ink injections were employed to provide an anatomical explanation of the localization of needle point and injection mass in the two types. It was concluded that the " cord-cerebrospinal fluid " and " cord " types of injection could be attributed to the penetration of a fasciculus by the needle point whence spread took place along the

inter-fibre spaces—the pathway of least resistance within the nerve. In the "blood" type injection the needle point lay within or just under the perineurium, the injection mass creating a limited subperineural space with variable but slight penetration of the fasciculus.

9. The employment of intraneural injections in the experimental investigation of tetanus and poliomyelitis is discussed in the light of these observations.

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METACHROMATIC BODIES IN THE BRAIN

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The purpose of this paper is to report the results of a study of the mucin, or mucin-like metachromatic substance, sometimes found in the white matter of the brain. This substance, occurring in small masses, has been referred to as " mucocytes." During the course of work on " grass sickness " in horses, these masses have been found ; it therefore has become urgent, before continuing this investigation, to determine whether these metachromatic masses or bodies are mere artefacts ; and if they are not artefacts, whether they are pathological or normal structures, and what their origin and nature may be. The term " mucocytes " is that most commonly used, but it may be misleadingly derivative, and will not be used here. Varying descriptions of this mucin-like substance have been given, and different views of its origin and significance expressed. It has generally been reported as occurring in the form of multilobulated grape-like areas throughout the white matter. Metachromatic bodies have been described by different workers as occurring in normal brains and in a large variety of pathological material, including senile dementia, epidemic encephalitis, Wilson's disease, paralysis agitans, and Schilder's disease. Different views as to the origin and significance have been expressed. The views on their origin which have been put forward fall roughly into two groups : first, it has been suggested that the metachromatic bodies are pathological, either of cellular origin or of extracellular origin ; secondly, that the metachromatic bodies are artefacts.

The literature contains references to the works of many authors who hold the opinion that metachromatic bodies are pathological and arise from cells. Grynfeltt (1923) found microscopical multilobate patches in the white matter of the central nervous system of patients with senile dementia, paralysis agitans, and Wilson's disease. Working in association with Pélissier and Pagès (1924), he also found these patches in dogs poisoned with formic acid. Pélissier (1924) studied similar areas in a case of " Wilson's disease following epidemic encephalitis." These areas gave the characteristic histo-chemical reactions of mucin. They were considered to be derived from glial cells. For these reasons Grynfeltt named them " mucocytes." Bailey and Schaltenbrand (1927) thought that the " mucocytic degeneration of Grynfeltt," and " acute swelling of the oligodendroglia " described by Penfield and Cone (1926) were identical. They studied a case of Schilder's disease, described the " mucocytic " degeneration present, and considered it an example of Grynfeltt's degeneration. Grinker and Stevens (1929) examined the brains in a laboratory collection from " cases of uræmia, arteriosclerosis, encephalomalacia, toxic and epidemic encephalitis, Schilder's disease, and a variety of other conditions." They also examined so-called " normal brains " from hospital cases where the disease process was non-cerebral. They found that in most of the brains examined both acute swelling of the oligodendroglia and " mucocytic " areas were present. They thought that the mucocytic areas were the result of degeneration of the oligodendroglia ; they believed that these cells, as they degenerate, swell and become mucoid, eventually bursting, and that they leave, as relics of themselves, coalescent masses of mucoid material.

Other authors have presented evidence in favour of their extra-cellular origin. Buscaino (1922), examining brains of patients with dementia præcox, and of animals poisoned with histamine, found free mucin in " grape-like areas of disintegration." He believed the masses were caused by abnormal amines circulating in the blood. He questioned the mucoid nature of the material, and named it " Substance X." He considered that it was derived either from degeneration of the myelin sheaths, or, less likely, from degeneration of ganglion cells. Lhermitte and others (1924) described mucin-like bodies in the brain of a patient with chronic epidemic encephalitis of Parkinsonian type, who died of

* Work undertaken on behalf of the Medical Research Council.

pulmonary tuberculosis. These bodies were free in the meshes of the white matter, showed no cell structure, and were spheroidal with irregular outlines. Their size was 20 to 30μ : the bodies stained with basic and not with acid dyes ; they gave the staining reaction of mucin, and were therefore thought to be mucin. Ferraro (1926, 1928) confirmed the metachromatic staining properties of the " mucocytes," and their solubility in chloroform, ether, pyridine, and partial solubility in acetone, absolute alcohol, and xylol. He found metachromatic concretions free in alcohol in which brains had been fixed ; he considered " mucocytes " and these concretions to be identical. He also stated that metachromatic bodies could always be found in frozen sections treated with alcohol. He concluded that the grape-like areas of disintegration of " mucocytes " in embedded tissue, and the structures in frozen sections were identical. He claimed that the " mucocytes " were derived from myelin sheaths, and that any involvement of the oligodendroglia was evidence of phagocytosis in these cells. He also observed that " mucocytes " were never obvious in formaldehyde-fixed sections unless alcohol had been allowed to act on them. Alcohol may, in Ferraro's opinion, act as a sensitizer for " otherwise undemonstrable lesions " consisting of " disintegrating lipoid or protein components of the myelin sheath." Thus, he considers that " mucocytes " are not necessarily artefacts. Their presence in normal brains does not invalidate this argument. It is possible that there are areas in a normal brain where the metabolism is to some degree altered without interfering with normal function : this alteration might lead to the presence of " mucocytes " in these areas. Unfortunately Ferraro did not specify the material he examined, and on which his conclusions were based.

The work briefly summarized above has favoured the biological origin of " mucocytes." Other investigators have brought forward evidence in favour of their being artefacts. Bielschowsky (1927) described areas of disintegration in the brain of a normal man free from pathological manifestations, executed at the age of 35. These areas were found in the centrum semi-ovale, corpus callosum, and areas where the grey and white matter are mingled. They were characterized by an absence of nuclei and by metachromatic staining properties. Bielschowsky thought that these mucous patches were derived from oligodendroglia by flowing out from these cells. The fact that there were fewer nuclei than normal was considered to be due partly to the degeneration of glial nuclei, and partly to an enormous increase in the volume of extra-vascular fluid. To what extent this effect was due to fixation was discussed but not decided. Other workers such as Salustri (1924) and Ansalone (1924) considered "mucocytes" to be artefacts. The reasons for their opinions were : first, the fact that the areas have been described in the brains of apparently healthy men and animals as well as in pathological material ; secondly, the fact that alcohol must be used to display them in frozen tissues.

It is impossible to know whether the appearances described in these papers refer to the same phenomenon ; illustrations of Pélissier's findings differ widely from those of Lhermitte or Grinker and Stevens. The details of histological technique are not always mentioned : the duration of time between the death of the subject and fixation of the tissues, the fixative used, and the embedding method, are all points frequently omitted. As will be shown below, the technique used has a bearing upon the histological appearances of the masses. On the whole the appearances of the masses, as seen in frozen and celloidin sections, are similar to the illustrations published by Grinker and Stevens ; while the same material prepared as paraffin wax sections resembles those of Grynfeltt and Pélissier.

Material and Findings

Metachromatic bodies were found in the brain of a man with Huntington's chorea, aged 57, and in two brains of young adult horses dead from grass sickness.* No pathological change was visible to the naked eye, either at the time of autopsy or when the brains were dissected after initial hardening. Throughout the investigation of these three brains, " normal " brains, both human and animal, were studied for comparison. These included : fifteen human brains of cases with non-cerebral lesions ; brains from two normal horses, two normal sheep, and eight normal rats. A large number of slides of many neurological conditions from Dr. J. G. Greenfield's collection were examined ; and various other histological material from the nervous systems of laboratory animals acquired during the course of other work was re-examined. The material was subjected to various procedures described below in order to elucidate the nature of these metachromatic bodies. The technical procedures are considered under the following six headings : (1) preparation of sections by different methods of embedding and application of a number of specific and non-specific stains ; (2) examination of alcohol as a sensitizer for the production of metachromatic bodies ; (3) examination of the reactions of metachromatic bodies to several solvents ; (4) examination of the

* Grass sickness is a disease of horses of unknown ætiology characterized by marked apathy and somnolence and by intestinal stasis ; it is commonly short, lasting twenty-four hours to three days, and frequently fatal.

effect of lipase digestion on metachromatic bodies ; (5) examination of factors, occurring between death and the preparation of sections, in the production of metachromatic bodies ; (6) examination of other possible factors.

Effect of Embedding and Staining Methods

Methods.—After fixation and hardening of the three affected brains in 10 per cent. formol saline, representative blocks from throughout the brain were embedded in celloidin and paraffin wax. Adjacent areas were also examined by the frozen section technique. Similar areas of " normal " human and horse brains were identically treated. The celloidin sections of brains exhibiting metachromatic bodies were stained with : Ehrlich's hæmatoxylin and eosin, Anderson's iron hæmatoxylin and van Gieson's stain, Mayer's muci-carmine, Best's carmine stain, Bennhold's congo red for amyloid, azan, Foot-Masson's trichrome stain (Foot, 1933), Gros' stain for axis cylinders, Loyez' stain for myelin, Kultchitsky-Pal modification of Weigert's method (Anderson, 1929), and thionin or toluidine blue stain. The method of staining with thionin or toluidine blue was as follows. Sections were cut at 10 to 12 μ and transferred to 1 per cent. HCl in 70 per cent. alcohol for five minutes. They were thoroughly washed in several changes of distilled water for ten minutes. They were stained for twenty minutes in 0·04 to 0·02 per cent. Grubler's thionin or in 1 per cent. Grubler's toluidine in distilled water at 50° C. and differentiated in 95 per cent. alcohol with or without 5 per cent. cajuput oil. After clearing in xylol they were mounted in Mersol (a proprietary immersion oil produced by Flatters and Garnett).

Celloidin sections of " normal " brains were stained with : Ehrlich's hæmatoxylin and eosin, Anderson's iron hæmatoxylin, and van Gieson's stain, Mallory's phosphotungstic acid hæmatoxylin, Foot-Masson's trichrome stain, Gros' stain, Loyez' stain, and thionin.

Paraffin sections of brains exhibiting metachromatic bodies and " normal " brains were stained with : Ehrlich's hæmatoxylin and eosin, thionin, and Mayer's muci-carmine stain.

Frozen sections from brains exhibiting metachromatic bodies were stained with : toluidine blue, Scharlach R (Herxheimer method) (Anderson, 1929), Cajal's stain for astrocytes, Hortega's stain for microglia, Bielschowsky's stain, Victoria blue, and Mayer's muci-carmine method ; while sections from normal brains were stained with : toluidine blue, Scharlach R, and Mayer's muci-carmine stain.

Findings.—In celloidin sections from brains containing metachromatic bodies, these bodies were seen as lobulated masses measuring on an average 100μ ; they were most vividly stained with thionin, the colour varying from pink to grey-brown ; with Ehrlich's hæmatoxylin and eosin, they stained a definite bluish purple. With Mayer's muci-carmine the masses were reddish purple, with hæmatoxylin alone there was no reddish coloration of the metachromatic bodies. Using Foot-Masson's and Azan stains they were colourless or pale pink, and with phosphotungstic acid hæmatoxylin colourless. Loyez' and Gros' stains did not reveal these masses, and sections so stained showed no abnormality. When thionin was used as a counter-stain on these sections the nerve fibres were seen in most instances to be apparently deflected to one side of the metachromatic bodies and occasionally a fibre passed through one. Kultchitsky-Pal stain showed no definite abnormality. None of the metachromatic bodies were bi-refringent, although small, bi-refringent particles were sometimes present between them (Table I and Figs. 1, 2, 3, and 4).

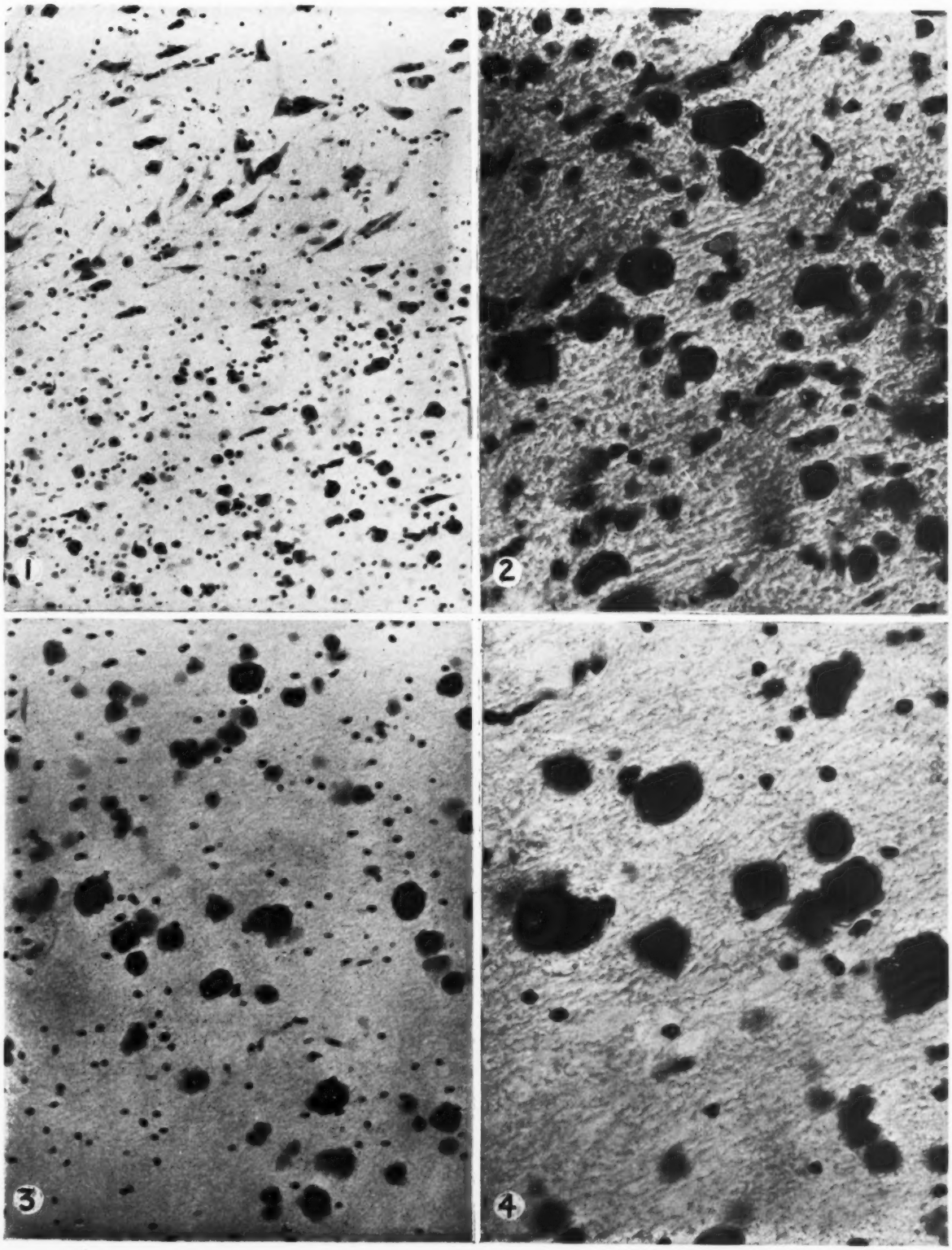
TABLE I

STAIN REACTIONS IN METACHROMATIC BODIES

Stain	Types of Section		
	Frozen	Paraffin	Celloidin
Thionin or toluidine	Pink	Red	Pink brown
Ehrlich's hæmatoxylin and eosin	Bluish	Blue-grey to colourless	Blue purple
Iron hæmatoxylin and van Gieson's stain			Blue purple to pale grey
Muci-carmine	Purple	Deep reddish purple	Reddish purple
Azan and Foot-Masson's stains			Pale pink to colourless

In the control " normal " human brains a very occasional pale structure of the shape of a " metachromatic body " was present but this was a rare finding. Such a structure stained a pale pink with thionin, bluish with hæmatoxylin and eosin. It did not stain with muci-carmine. In the " normal " horse brain structures as described above were a little more numerous and definite but were still very infrequent, in marked distinction to the very large numbers found in any microscopic field in affected horses.

When the paraffin sections of the brains containing metachromatic bodies were examined immediately after mounting, it was seen that some of the bodies were sufficiently large to be visible to the naked eye, measuring 300 to 500μ in diameter. They were coloured a vivid red with thionin, reddish purple with Mayer's muci-carmine, and greyish with Ehrlich's hæmatoxylin and eosin. A short time after being mounted in Mersol or Canada balsam,



(For legends see page 104)

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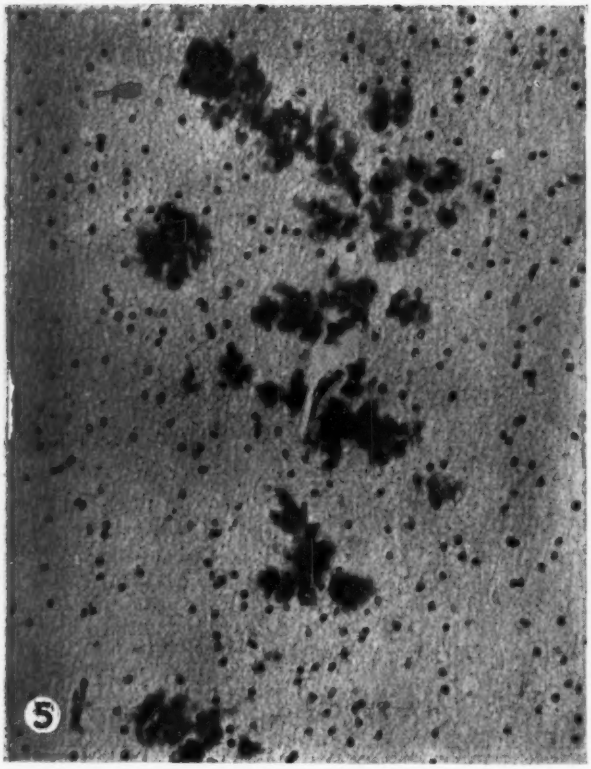
COLORADO
SCHOOL OF



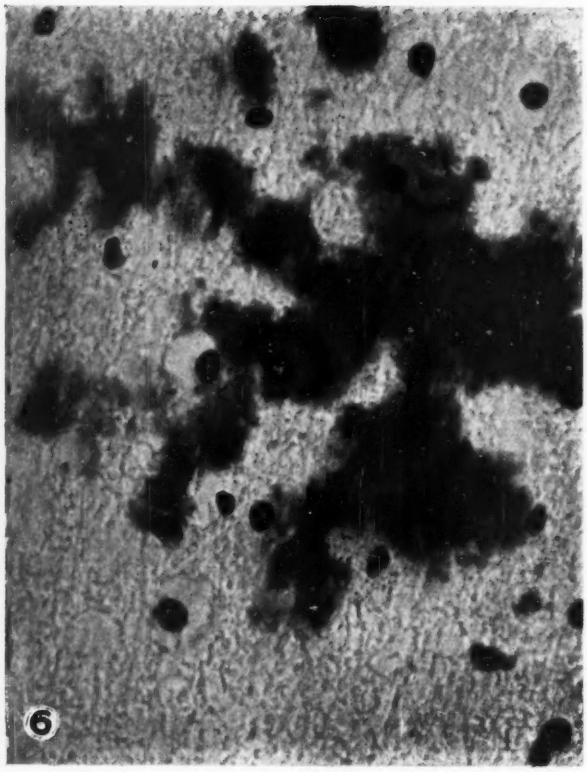


FIG. 1.—Metachromatic bodies in the white matter of the brain of a horse dying from grass sickness. (Celloidin section, × 200.)

FIG. 2.—Metachromatic bodies in the white matter of the brain of a horse dying from grass sickness. (Celloidin section, × 400.)

FIG. 3.—Metachromatic bodies in the white matter of the brain of a man with Huntington's chorea. (Celloidin section, × 350.)

FIG. 4.—Metachromatic bodies in the white matter of the brain of a man with Huntington's chorea. (Celloidin section, × 600.)

FIG. 5.—Metachromatic bodies in the white matter of the brain of a horse dying from grass sickness. (Paraffin section, × 200.)

FIG. 6.—Metachromatic bodies in the white matter of the brain of a horse dying from grass sickness. (Paraffin section, × 650.)

usually about thirty minutes, these masses had faded or dissolved, and irregular pale areas in the meshwork of the white matter remained in their place. These areas were markedly larger than the masses seen in celloidin sections, and fewer in number, suggesting that smaller masses may have become diffluent and confluent. They were bi-refringent both before and after staining; this bi-refringence disappeared with the "fading" of the masses. No other bi-refringent material was present in the sections (Table I, and Figs. 5 and 6). In the "normal" brains no appearances such as have been described above were found.

When frozen sections from the brains containing metachromatic bodies were stained with toluidine blue the bodies, similar to those seen in celloidin sections, were stained a definite pink colour. Scharlach R revealed no sudanophil material; no other abnormality was detected by use of the other stains. The metachromatic bodies were bi-refringent; no other bi-refringent material was present (Table I). In approximately half the "normal" brains examined, sections stained with toluidine revealed pinkish lobulated shreds along myelin tracts. A number of small pink bodies were also present. In the "normal" horse brain similar sections contained more definite pink multilobate masses. It has generally been accepted that such masses are derived from myelin. These bodies were not nearly so numerous as the metachromatic bodies in the affected brain; they tended to be smaller and more elongated, but otherwise in appearance they resembled the metachromatic bodies. They did not stain with muci-carmine; they were mostly bi-refringent (Table II).

Sensitization of Metachromatic Bodies by Alcohol

Method.—Frozen sections were stained with toluidine blue, in the following manners: directly, omitting any form of alcohol before staining, after fifteen minutes in absolute alcohol, after twenty-four hours in absolute alcohol, and lastly after forty-eight hours in absolute alcohol.

Findings.—In brains exhibiting metachromatic bodies in which the sections were stained before treating with alcohol some pale indefinite pink patches were seen in the white matter. If the sections were stained after being in alcohol for fifteen minutes, these areas were far more clearly seen and stained more positively, as is characteristic of the metachromatic bodies. When the sections were in alcohol twenty-four hours before staining, the appearance was similar to that after only fifteen minutes in alcohol. Again, if the sections were in alcohol forty-eight hours before staining, the appearance was similar. Increasingly long periods in alcohol did not appear to alter the staining or size of the metachromatic bodies.

Sections from "normal" brains stained before treatment in alcohol showed some pale indefinite patches as in the affected brains similarly treated. Fifteen minutes in alcohol, in about 50 per cent. of the brains examined, was productive of pinkish shreds, generally considered to be derived from myelin. Such shreds or masses were more definitely pink if the sections had been immersed in alcohol

Table II

Points of Comparison between Myelin Substance and Metachromatic Bodies

Features	"Myelin substance" bodies	"Metachromatic" bodies
Number	Usually few	Very many
Distribution	Throughout white matter	Throughout white matter
Size	Variable: mainly 10–15 μ; few may be 100 μ	Variable: 10–100 μ; majority 50–100 μ
Shape	Single or multilobated bodies, elongated lobated strands	Multilobated, spherical or elongated along fibre tracts.
Occurrence:		
Frozen section	Present	Present
Paraffin section	Absent	Present
Celloidin	Occasional single form	Present
Stain reactions in frozen sections:		
Toluidine blue	Present	Present
Muci-carmine	Absent	Present
Bi-refringence	Present	Present

for twenty-four hours : and these masses resembled metachromatic bodies in structure. They were still not so numerous, and were found in only about 50 per cent. of the brains examined. In sections after more prolonged immersion in alcohol, up to forty-eight hours, fewer myelin-shreds were found than in those immersed for twenty-four hours. After increasingly long periods in the alcohol the " myelin substance " did not appear. No concretions were found in the alcohol used to treat the sections, nor in alcohol in which the blocks of tissue were kept for twenty-four hours.

Solubility of Metachromatic Bodies in Solvents

Method.—Frozen and celloidin sections were placed in chloroform, ether, or acetone for fifteen minutes and then stained with toluidine blue ; or treated with alcohol, and then exposed severally to chloroform, ether, or acetone for fifteen minutes and then stained with toluidine blue.

Findings.—When the frozen sections were subjected to the action of one of these liquids, chloroform, ether, or acetone, before alcohol treatment and staining, none of the liquids had any apparent effect on the metachromatic bodies. When the sections were first put in one of the liquids, and then stained, the metachromatic bodies were seen to be soluble to some extent. With chloroform there was a partial solution of the metachromatic bodies immediately, but the process was not completed until some days after mounting : then " fatty " globules could be seen on the surface of the sections. With ether and, to a lesser extent, acetone, there was a partial solution of the metachromatic bodies with the production of a blurred outline. The metachromatic bodies in frozen sections stained with toluidine faded some weeks after mounting, and there was also some diffusion into the mounting medium : " Mersol " or balsam.

In celloidin sections the metachromatic bodies were far more resistant to the liquids and did not diffuse. This result was anticipated, as the bodies had already remained distinct after prolonged treatment in alcohol and ether during the embedding processes. It is of interest that the myelin material of the " normal " brains behaved in a manner similar to that of the metachromatic bodies found in the pathological brains, except that it was more readily soluble in the liquids tested.

Lipase Digestion

Method.—Frozen and celloidin sections of the brains exhibiting metachromatic bodies and " normal " brains were incubated for times varying from thirty minutes to seventeen hours in a solution of lipase and sodium taurocholate buffered to a *p*H of 8·2 (100 ml. of 20 per cent. lipase solution and 50 ml. of 1 per cent. sodium taurocholate). The sections were then washed, put in alcohol, and stained with toluidine or thionin, Ehrlich's hæmatoxylin and eosin, or Mayer's muci-carmine.

Findings.—It was thought that some indication of the composition of the metachromatic bodies might be gained by establishing their reaction to enzymes. It was recognized that the tissues available had already been altered by fixation, dehydration, and embedding, and that any action on them would be different from that of the enzyme on fresh tissue. Nevertheless it seemed possible that some constant reaction to an enzyme should prove of value.

It was found that in frozen sections the metachromatic bodies were mostly digested away to leave non-staining areas, possibly holes. Where digestion was incomplete the bodies had become ragged looking with a blurred outline. They stained pink with toluidine and pale purple with muci-carmine.

In celloidin sections, instead of the homogeneous staining appearance of the metachromatic bodies usually noted, there was a coarsely granular denseness in the centre of the mass, surrounded by a clear area. These granules stained deeply with thionin, hæmatoxylin and eosin, and muci-carmine, leaving a clear non-staining area around. The effect of the lipase on the rest of the section was to show up the detail of glial nuclei, and to a lesser extent the nerve cells, more clearly than usual.

In the frozen section of the " normal " brains the effect of lipase on the myelin substance was to " digest " it away almost completely. The shreds remaining were blurred or stained faintly.

The effects described above were seen most clearly after seven hours' incubation. When the sections were incubated for a shorter time they showed similar changes, but to a slighter degree ; after more than seven hours the entire sections became somewhat hazy, and metachromatic masses could not be distinguished.

Fixation Factors Tested

In order to find out if any factors occurring between the death of the animal and the staining of its tissues played a part in the genesis of metachromatic bodies, a further series of brains was investigated. In these experiments brains were obtained from humans, sheep, and rats. The human material came from patients dying from causes that were primarily non-cerebral, namely, reticulo-endotheliosis, tuberculosis, heart failure (2), carcinoma of stomach, carcinoma of prostate, and pneumonia. They were obtained as early as possible, and not later then twenty-four hours after death. The two sheep used were healthy ; they were killed by nembutal and bleeding. The rats used were

killed by chloroform and the brains were removed and treated immediately as described below.

As it had been suggested that metachromatic bodies occurred more commonly in the heat of the summer, or when the material was fixed under warm conditions, the effects of temperature were investigated. The concentration of the formalin which we used as a fixative was investigated, and also the lapse of time between death and fixation. The effects of much handling and washing of the material was studied, and also the length of time of preservation in formalin.

Method.—One human brain and four rat brains were fixed in 20 per cent. formol saline for times varying from one to fourteen hours; they were removed from the fixative, put in the incubator at 37° C. for five hours, and then refixed in 20 per cent. formol saline. One human brain and two rat brains were also put in the incubator at 37° C. for five hours, and then fixed in 20 per cent. formol saline. Two rat brains were put in the refrigerator for four to eight hours immediately after autopsy, and then fixed in 20 per cent. formol saline (Table III). From these brains sections were prepared.

To determine the effect of formalin concentration, the following methods were adopted. Very large slices from "normal" human and horse brains were fixed in 5 per cent., 10 per cent., and 20 per cent. formalin in water (May and Baker's formalin); and similar slices in 5 per cent., 10 per cent., and 20 per cent. formol saline (formalin in 1·75 per cent. NaCl). Sections were prepared.

To study the effect of delay in fixation, five human brains and brains from two normal healthy sheep were obtained immediately after death. In each case the brain was divided longitudinally into two halves. Throughout the experiment one half was kept in the refrigerator, the other at laboratory temperature, both in airtight containers. Large slices from each half were fixed in 20 per cent. formol saline at intervals of approximately ten hours, up to one hundred and twenty hours. Again one "normal" brain was divided longitudinally, of which one half was washed for ten minutes in tap water before fixation in 20 per cent. formol saline, and the other half was "handled" considerably before fixation in 10 per cent. formol saline. Healthy brains fixed for varying lengths of time in formalin—four days to several years—were examined.

Findings.—The effect of varying temperatures during fixation was of interest. In none of the brains submitted to the temperature variations were metachromatic bodies found.

In brains submitted to different concentrations of formalin and formol saline no metachromatic bodies were to be seen.

It was considered that if these metachromatic bodies were fixation artefacts, delay in fixation would be their most probable cause. Paraffin and celloidin sections of the brains from the delayed fixation experiments showed no metachromatic bodies. In the frozen sections there were a few of the pink bodies derived from myelin already referred to. Collected sections from other human material, where the interval between death and

TABLE III

TEMPERATURE VARIATIONS IN FIXATION OF BRAINS

Material	Cause of death	Autopsy	Fixation	Incubator	Refrigerator	Fixative
1 human brain ..	Reticulo-endotheliosis	Within 12 hours of death	For 4 hours in 20% formol saline	For 5 hours		Refixed in 20% formol saline
4 rat brains	Chloroform	Immediately	For 1–4 hours in 20% formol saline	For 5 hours		Refixed in 20% formol saline
1 human brain ..	Tuberculosis	Within 12 hours		For 5 hours		Fixed in 20% formol saline
2 rat brains	Chloroform	Immediately		For 5 hours		Fixed in 20% formol saline
5 human brains ..	Tuberculosis Pneumonia Heart failure Carcinoma of prostate Carcinoma of stomach	Within 24 hours of death			10–110 hours	Fixed in 20% formol saline
2 rat brains	Chloroform	Immediately			4–8 hours	Fixed in 20% formol saline

the autopsy varied from twelve to sixty hours, were also examined. No metachromatic bodies were found in these sections.

Neither handling of the brain at autopsy, nor the length of time in formalin—four days to several years—were found to be associated with the occurrence of metachromatic bodies in either celloidin or paraffin sections.

Other Factors

When the cause of death was studied as a possible factor, collected celloidin sections illustrating widely different disease conditions, mainly but not entirely of a neurological nature, were examined. These specimens included all the common degenerative, vascular, infectious, and neoplastic neurological conditions. Metachromatic bodies were not found so far in any sections other than those described in this paper. " Holes " were frequently present in the white matter, but there was no staining in these areas. In many cases the appearance was that usually associated with œdema.

It was considered possible that metachromatic bodies might arise in a consequence of disordered metabolism resulting in a necrobiotic phenomenon. To investigate this aspect of the problem sections from the brains of patients dying in a state of coma, anoxæmia, starvation, or dehydration were prepared and examined. No metachromatic bodies were seen.

Again, collected sections of brains of patients varying in age from infancy to eighty years at death were examined. No metachromatic bodies were seen. The age of the patient with Huntington's chorea was fifty-seven. The horses were young adults.

Brains of mice, rats, guinea-pigs, ferrets, and sheep were examined without showing more than the occasional pale form of metachromatic body already described in the normal brain.

Discussion

Sections from the brain of a man with Huntington's chorea and from the brains of two horses dying from grass sickness were prepared in celloidin, in paraffin wax and by freezing. In the three cases frozen and celloidin sections of all parts of the brain contained very large numbers of metachromatic multilobate masses. These masses were limited to the white matter, extending into the grey only in association with fibre tracts.

The masses were clearly the substance described as " mucocytes " by Grynfeltt. They were most numerous throughout the cerebrum and cerebellum, and less plentiful in the brain stem and medulla. They practically equalled the number of glial nuclei in the field (Figs. 1 and 3). Many seemed to be formed by the conglomeration of separate bodies, which produced a multilobate mulberry effect (Figs. 2 and 4). This lobulated appearance was present even when the masses remained unstained. The diameter varied between 10 and 150μ, with the majority between 100 and 150μ. Where the mass was more elongated than rounded, the long axis was invariably directed along the length of the nerve fibres, and never transversely. No nuclei or remains of nuclei were seen in the masses ; when glial nuclei appeared to be involved in the masses they were optically readily separable from it. In view of the very large number of metachromatic bodies present, such a superficial association between glial nuclei and the bodies was inevitable. In the paraffin sections the areas were markedly larger than the metachromatic bodies in celloidin sections, and fewer in number (Figs. 5 and 6). In the horses no other abnormality was observed : vessels, neurones, axis cylinders, and myelin sheaths all appeared normal. There was no increase in glial cells ; this was confirmed by nuclear counts in similar areas of affected and normal horse brains. There was no change in the oligodendroglia, and no staining of the cytoplasm of these cells with muci-carmine. In the brain of the case of Huntington's chorea the pathological changes were confined to the grey matter. They were only those associated with the condition.

In " affected " brains metachromatic bodies appear in very large numbers. They can be shown to stain with basic dyes, and may therefore be assumed to be acid in nature. They stain metachromatically with thionin and toluidine, and stain with muci-carmine ; they contain, therefore, a substance or substances similar to those found in mucin. They do not give the stain reactions of fat, glycogen, or amyloid. Before staining, treatment with alcohol is necessary to show up the metachromatic bodies in a definite form. They are to some extent soluble in chloroform, acetone, xylol, and ether, but they are sufficiently insoluble in ether to remain present during the clearing and embedding processes in celloidin and paraffin techniques. In frozen sections they are bi-refringent, unless acted on by alcohol forty-eight hours or longer. They are also bi-refringent in paraffin sections. The possibility of " metachromatic " bodies being entirely due to fixation has been considered. If, as some observers have thought, they are due to fixation artefacts only, it should be possible to produce metachromatic bodies by reproducing the conditions of fixation under which they occurred. A wide range of variations in the technique of fixation has been used, but no factors were found which

produced these bodies. The cause of death, the condition before death, and also age and species specificity have been examined ; these factors could not be related to the presence of the metachromatic masses.

The superficial resemblance between the metachromatic masses and the mucoid degeneration present in certain forms of Schilder's disease was observed, but many differences must be noted. In these cases of Schilder's disease there are marked changes which include degeneration of myelin sheaths, mucoid degeneration of oligodendrogial cells, and a possible presence of compound granular cells. There were no such gross alterations in the brains described here. The appearences of the " metachromatic bodies " and of the mucoid degeneration in such a case of Schilder's disease have some resemblance when stained by thionin, but the use of a trichromic stain such as azan reveals the " metachromatic bodies " as pale pink or colourless, as opposed to the definite pink and blue mucoid masses in such forms of Schilder's disease. Corpora amylacea cannot be confused with the " metachromatic bodies." They may be present at the same time, and the corpora amylacea can be seen to be more spherical and solid, and to present different staining reactions as they are not metachromatic.

In frozen sections of " normal " brains shreds of a material may be seen, which are generally considered to arise from myelin. These also stain metachromatically with thionin or toluidine, but do not stain with muci-carmine. They are soluble in chloroform, ether, acetone and xylol, and are bi-refringent. They do not appear in paraffin sections, and only very occasionally and sparsely in celloidin preparations. The resemblance between the form and character of the metachromatic bodies, and the myelin-derivatives in normal brains, is too marked to be accidental. The main differences between the ordinary myelin derivatives and the metachromatic bodies are the greater number of metachromatic bodies compared with the few myelin shreds in frozen sections, the persistence of the metachromatic bodies in paraffin and celloidin preparations, and the fact that they stain with muci-carmine (Table II).

It may, then, be reasonably assumed that the metachromatic bodies are derived from the myelin, or from the ground substance of the brain. This view is strengthened by the observation that the acid reaction of the bodies, and their specific reactions with toluidine and muci-carmine are like those of polysaccharides and their derivatives, particularly those that are sulphated, present in mucus, cartilage, and other intercellular structures. The fact that they appear only after treatment with alcohol suggests that a disturbance in the colloid disperse suspension of the complex compounds consisting of tri-glycerine, carbohydrates, and nitrogenous substances present in myelin, must be brought about first. A pre-existing disturbance in these substances may explain an alteration in the number and character of the metachromatic bodies. The most important change would seem to be the solubility of the myelin derivatives : the more soluble is the myelin in shreds, the less soluble is the substance found as metachromatic bodies.

Further investigations are being made on a similar line, with particular attention being paid to obtaining fresh material of varied disorders and diseases. The examination of such tissues at set times after death and fixation, and immediately after staining, standardizes the result. Substance present in the freshly prepared slide may disappear in the course of time. The hydrogen ion concentration of the tissue examined, or of a reagent used in the preparation of sections, may contribute to the appearance of metachromatic bodies.

Conclusions

Metachromatic bodies are considered to be derived from myelin or from the ground substances of the brain ; they are less soluble in alcohol, ether, chloroform or acetone, than myelin, and share characteristics with mucus and similar substances.

At the present stage of investigation there is nothing to show that the metachromatic bodies are entirely artefacts, in view of the inconstancy of their occurrence, and the failure to produce them deliberately by varying laboratory technique. The process leading to the formation of these bodies is diffuse, affecting all or the greater part of the white matter in the brain ; but a pathological agent or patho-physiological process leading to their appearance has not been found.

It is suggested that for the production of manifest metachromatic bodies the following conditions obtain : an alteration of solubility of myelin or the ground substance, arising from metabolic factors before death, or resulting from factors in the time after death. A minor variant in the treatment of the material after death cannot be excluded as being contributory.

Summary

Three brains exhibiting " metachromatic bodies " were examined.

" Normal " brains were subjected to different technical procedures to find out if such metachromatic bodies were fixation or staining artefacts.

A search was made for metachromatic bodies in brains from a large variety of conditions.

The origin of metachromatic bodies was discussed.

My thanks are due to Dr. E. Arnold Carmichael, in whose department these investigations were carried out, for his help in writing this paper. I also wish to thank Dr. J. G. Greenfield for permission to use his material and for his advice; Professor Russell Greig for his material; and Dr. Peter W. Nathan for his helpful criticism. I am also grateful to Mr. James Mills for his generous help with technical problems, and to Miss Vera Burgess for her able co-operation.

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ELECTRICAL ACTIVITY OF THE NEOSTRIATUM, PALEOSTRIATUM, AND NEIGHBOURING STRUCTURES IN PARKINSONISM AND HEMIBALLISMUS*

BY

RUSSELL MEYERS, ROBERT HAYNE, and JOHN KNOTT

The present investigation represents an extension of an inquiry into the electrical potentials of the basal ganglia and exposed cerebral cortex in Parkinsonism reported upon by one of us (R.M.) in 1941. At that time, the first recordings from the human caudate nucleus were obtained by means of an Adrian-Bronk needle inserted under direct inspection into the head of the nucleus and supported *in situ* by the operator's hand. The electrocaudatograms thus obtained were characterized by a faster frequency and lower amplitude than corresponding electrocorticograms recorded by means of concentric electrodes applied directly to various parts of the convexity of the frontal lobe. The relative crudity of these early attempts gave rise to the misgiving that the experimental findings might have been much more dependent upon the recording techniques employed than upon the pathophysiologic phenomena presumed to be under inquiry. Further exploration of the problem by more reliable techniques therefore appeared desirable.

Method

Before the institution of the experimental routine in each patient, all medication was discontinued for several days. Under local infiltration anæsthesia of the scalp with 1 per cent. procaine hydrochloride, paired burr openings were made through the right and left anterior vertical regions of the skull. The position of the opening on each side was so planned as to lie directly above the head of the caudate nucleus. The dura and piarachnoid were suitably incised and the scalp was closed in two layers with black silk. At a later time, usually within two hours of trepanation, a slender plastic shaft equipped with eight ring-type "pick-up" electrodes was passed through one of the burr openings. The direction given to the needle and its distance from the surface were such as to place the electrodes in one or more of the following subcortical structures in each subject: the head of the caudate nucleus, the putamen, crus II of the globus pallidus, the subcallosal bundle, the anterior portion of the body of the corpus callosum, the substantia medullaris of the corona radiata, the olfactory area, the cortex of the olfactory sulcus, the hypothalamic area, and the infracallosal portion of the cingulate gyrus (Fig. 1).

The electrode shaft was of the same design as that recently employed by one of us (R.H.) collaborating with Belinson and Gibbs (Hayne and others, in the press) in a study of the electrical activity of the thalamus in epileptic patients. The length of the shaft was 10·5 cm. and its diameter 2·3 mm. Eight silver rings, each 2·5 mm. wide and separated by 3·0 mm. from its neighbours, served as pick-up electrodes. These were disposed along the distal half of the non-conducting plastic shaft. Within the shaft, an insulated wire coursed from each of the eight ring-type electrodes and emerged from the hub. To the free-hanging distal end of each wire a phone-tip jack capable of being plugged into the electrode junction box of a recording unit was attached.

Bipolar and monopolar recordings (the latter employing the ears as reference electrode) were made from both the standard electro-encephalogram scalp leads* and the subcortical leads in the corpus striatum by means of a Grass III-A, eight-channel ink-writing electroencephalograph. In the earlier studies of the series, simultaneous recordings of the mathematically possible combinations of the scalp and subcortical leads were made. As the inquiry proceeded, it appeared warrantable to eliminate certain pick-up combinations from the schedule, so that only those which yielded the most characteristic and/or most useful localizing data were retained for subsequent experiments. Thus, in the case of the subcortical leads, bipolar combinations of (*a*) immediately neighbouring ring electrodes and (*b*) those removed from one another by a single intervening ring proved most practicable.

After the desired electrical recordings were obtained from the patient under study and while the electrode shaft was still *in situ*, pneumoencephalography was carried out. The purpose of the latter procedure was to help ascertain as accurately as possible, short of necropsy examination, the position occupied by each of the eight electrodes. The identification of the anatomical sites of the several electrodes was determined

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* The "standard" placements of scalp leads are those attached to the left and right frontal, central, occipital, and temporal regions. These have been designated in the present paper by the abbreviations LF., RF., LP., RP., LO., RO., LT., and RT. The symbol "-e" indicates that a monopolar technique was employed, the reference electrode being attached to the lobe of the ear.

by the following means. A normal adult brain, freshly removed at autopsy, was suspended by a gauze hammock in 10 per cent. formalin solution until well hardened, and later sectioned through the mid-sagittal plane. The body and anterior horn of the right lateral ventricle were exposed to view by removal of the septum pellucidum and suitable portions of the fornix and corpus callosum. A " grid " consisting of a series of silk threads strung in parallel at intervals of 0·5 cm. was then superimposed upon the mesial surface of the right hemisphere in such fashion that its chords were approximately perpendicular to the antero-posterior axis of the hemisphere. The chord corresponding to the most rostral limit of the anterior horn was arbitrarily designated number 1. Succeeding chords were designated by the numbers 2, 3, 4, . . . 15. Each thread was regarded as the determinant of a separate coronal plane of the hemisphere. The brain was now suitably marked in correspondence with the determinants and was placed against a specially designed near-precision apparatus by means of which the indicated serial coronal sections were prepared at intervals of 0·5 cm. The coronal sections were identified by numbers corresponding to their respective chords and were separately photographed.

By comparing the position of the electrode shaft, as revealed in the lateral view of the patient's pneumoencephalogram, with a photograph of the grid-covered mesial aspect of the brain it was possible to determine with fair accuracy the chord (or chords) with which the axis of the electrode shaft most closely coincided. The photograph of the appropriate coronal plane was then compared with the axis of the electrode shaft and with the positions of the several ring-type electrodes as revealed in the antero-posterior view of the patient's pneumoencephalogram. On the basis of such data, the position of each of the eight ring-type electrodes was ascertained.

The ring-type electrode most distal to the hub of the shaft was arbitrarily designated number 1. The others, progressing in order toward the hub, were numbered 2, 3, 4, 5, 6, 7, and 8. Thus, for example, in the illustrations which follow 2–4 signifies that the bipolar technique was used and that the pick-up electrodes employed in obtaining the electrogram were the second and the fourth rings from the distal end of the shaft. Similarly, 3 -e signifies that a monopolar technique was used and that the electrodes employed were the third from the distal end of the shaft and that attached to the ipsilateral ear.

It was possible in one instance to verify directly the structures through which the electrode shaft had passed. This was in patient A.L., a 42-year old housewife who died four days following operation for the relief of Parkinsonian tremors. She had undergone extirpation of the head of the caudate nucleus, section of fibres of the anterior limb of the internal capsule, and interruption of pallido-fugal fibres. Her postoperative course was generally satisfactory except for short-lived and irregular bouts of vomiting. In one of the latter episodes she aspirated vomitus and died of asphyxia. Post-mortem examination confirmed that the electrode shafts used in two separate experiments on this patient had traversed the caudate nucleus and crus II of the globus pallidus (Fig. 2).

Experimental Group.—The subjects constituting the experimental group* dealt with in this paper consisted of eleven patients suffering from " extrapyramidal disorders." In nine of these, the diagnosis of Parkinsonism of either post-encephalitic or " idiopathic " varieties was made. The tenth patient had a chronic left hemiparesis and hemi-Parkinsonism consequent upon severe craniocerebral trauma. The eleventh was a 50-year old woman with moderately severe but well controlled diabetes who, ten weeks before the present study, suddenly developed a violent hemiballismus of the limbs of the left side. In each instance the experimental nature of the investigation was explained to the subject and full consent obtained for the study.

The plan of procedure consisted in recording electroencephalograms from the standard scalp leads and from the right and left subcortical structures of each patient. Since in all but two instances unilateral placement of the electrode shaft was employed, the procedure required as a routine two separate experiments upon each subject. In order to allow for clinical recovery from the effects of pneumoencephalography, therefore, several days were allowed to intervene between experiments. In all, twenty-one experiments were carried out on the experimental subjects : two on each of eight patients, one on each of two, and three on the remaining patient (see Table).

The recordings derived from each cerebral structure were separately analyzed with respect to (*a*) frequency, (*b*) voltage, and (*c*) relative polarity of waves. Those obtained from each subject were then compared with one another and also with those from all other subjects in both the control and experimental groups and an attempt was made to ascertain whether consistent relationships existed.

Results

Analysis of the electrical records derived from leads placed on the scalp, in the corpus striatum, and over the muscles of the extremities led to the following series of descriptions and tentative formulations.

Variations in Frequency.—Variations in the frequency of waves derived from mono- and bipolar scalp electrodes are, as is well known,

* **Controls.**—In addition to those of the experimental group, eleven control subjects, none of whom was considered to be suffering from " organic " disease of the brain, were studied in a manner similar to that employed for the experimental subjects. Seven of these were afflicted with intractable pain (pelvic carcinoma, phantom limb, etc.) and four with psychologic aberrations. All control subjects had been previously accepted for prefrontal lobotomy and studies of their cerebral action potentials were carried out several days prior to operation. The data referable to the control group have been made the basis of separate reports (Hayne and others, in the press ; Meyers and Hayne, 1948). In the majority of instances the frequencies of waves recorded in the several control subjects were slightly lower than those generally encountered among " normals."

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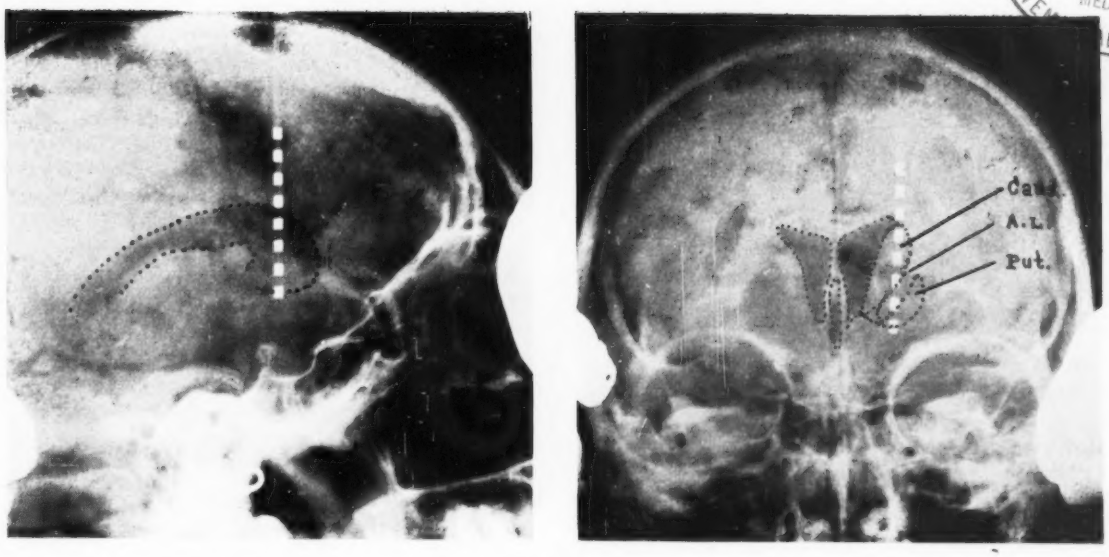

FIG. 1.—Pneumoencephalograms of patient L.P. The ventricles have been outlined with small dots for greater ease of identification. The configuration of the main structures encountered at the coronal plane traversed by the electrode shaft is similarly delineated.

Caud.=head of caudate nucleus; A.L.=anterior limb of internal capsule; Put.=putamen. The placement of the ring electrodes in this case was considered to be as follows: 1—putamen; 2—anterior limb of internal capsule; 3—margin of head of caudate nucleus and anterior limb of internal capsule; 4 and 5—head of caudate nucleus; 6—subcallosal bundle; 7—corpus callosum; 8—corona radiata, deep in hemisphere.

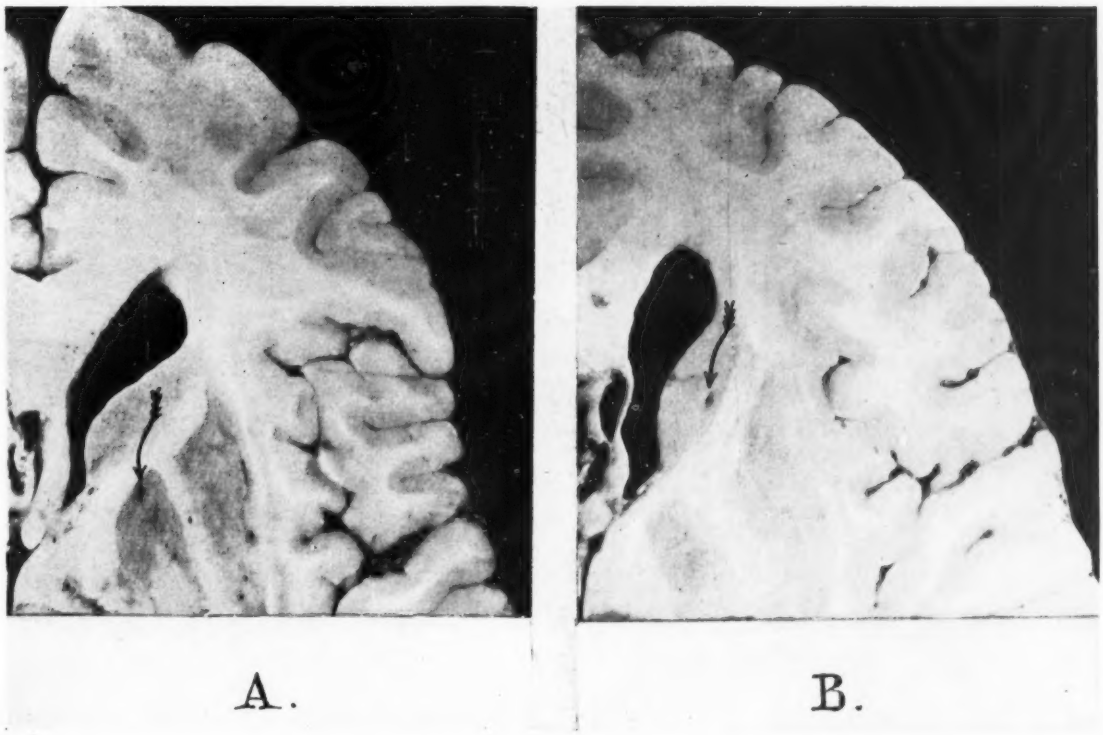

FIG. 2.—Horizontal sections of right hemisphere of patient A.L., illustrating tracts produced by electrode shafts. In A, arrow points to lesion in crus II of the globus pallidus. In B, arrow points to lesion in the head of the caudate nucleus.

encountered from subject to subject and from time to time within a given subject. Similar variations evidently prevail in respect of wave frequencies derived from leads located in the neostriatum, the paleostriatum, and their immediate neighbourhoods. The pertinent data is summarized in the Table, in which the *central tendencies** of the wave frequencies derived from the scalp electrodes have been arbitrarily arranged in ascending order. A comparison of the central tendencies and ranges of wave frequencies in the control and experimental groups disclosed no significant disparities. In view of the familiar histologic and (presumed) functional derangements of the strio-pallidal apparatus in the so-called extrapyramidal diseases, this was a somewhat unexpected disclosure.

* Ranges of means based on samples of one second's duration. A *range* is given in view of the fact that the frequencies and amplitudes varied from lead to lead as well as from subject to subject and from time to time within a given subject.

Relative Frequencies.—Reference to the Table and to Fig. 3 discloses that in any given subject the frequency of the bipolar subcortical waves exceeded by one to eight cycles per second that characteristic

TABLE

CENTRAL TENDENCIES OF WAVE FREQUENCIES RECORDED IN EACH PATIENT FROM SCALP AND SUBCORTICAL ELECTRODES BY MONO- AND BIPOLAR TECHNIQUES

Patient	Sex	Age	Diagnosis	Tremor*	Rigidity*	Experiment No.	Scalp Leads	Subcortical Leads	
							Mono- and Bipolar	Mono-polar	Bipolar
A.G.	M.	52	Prksn.	+	+++	1	7 – 7½	7 – 8	10 –12
						2	7 – 8	7½– 8	10½–12
R.C.	M.	43	Prksn.	++	+++	1	7 – 8	7½– 8	8 – 8½
						2	7 – 8	8½– 9½	10 –12
W.G.	F.	38	Prksn.	++ (Lt.)	++	1	7½– 8½	8 – 9	7 – 8
						2	8 – 9	8½– 9	8 – 9
						3	8 – 9	8½– 9	8 – 9
F.B.	F.	50	Hemibal.	+++ (Lt.)	0	1	7½– 8½	8 – 8½	10½–11
A.L.	F.	42	Prksn.	+++	++	1	8 – 9½	8½–11	9½–11½
						2	8½–10	9½–11	9½–11½
E.G.	F.	65	Prksn.	+++	++	1	8 – 9	8 – 9½	15 –17
						2	8½– 9½	None recorded	16 –17
L.P.	M.	47	Prksn.	++ (Rt.)	++	1	8 – 9½	8½– 9½	9½–10½
L.D.	M.	29	Hemi-Prksn. (trauma)	+++ (Lt.)	++++ (Lt.)	1	8 – 9	8 – 9	11 –12
						2	8½– 9	8 – 9½	11 –13
W.H.	M.	36	Prksn.	+	++++	1	8½– 9	8 – 9	11 –12
						2	8½– 9	11 –12	12 –14
C.H.	M.	48	Prksn.	++++	+++	1	9 – 9½	8½– 9	10 –11
						2	9 – 9½	8½–10	11½–14
W.B.	M.	42	Prksn.	++++	+++	1	9½–10½	9 –10	8 –10
						2	9½–10½	9½–10½	9½–12

* Unless designated by (Rt) or (Lt), the disorder may be presumed to have obtained bilaterally. Tremor and rigidity are here estimated as if on a continuum, ranging from one plus (slight) to four plus (very marked).

of waves derived from scalp leads, regardless of whether obtained by the mono- or bipolar techniques. In addition, those experimental subjects exhibiting a relatively low frequency of waves derived from the scalp leads (for example, 7–8 per second) exhibited in the concomitantly-recorded subcortical waves obtained by the bipolar technique a frequency relatively slower than that of the corresponding subcortical waves obtained in their fellow subjects. All these data were virtually the same as those derived from the control cases.

Amplitude.—The amplitude of waves obtained from the scalp electrodes varied from subject to subject and from time to time within each subject. The over-all *central tendency*, 35–75 μv, corresponded closely to that encountered in control subjects when comparable recording techniques were employed. Similar variations from subject to subject and from time to time within a given subject prevailed in respect to the wave amplitudes obtained by the bipolar technique from electrodes located in the neo- and paleo-striatum and their neighbouring tissues. The over-all *central tendency* of the amplitude of such subcortical waves obtained by the bipolar technique approximated 15–25 μv. This observation conformed closely to that demonstrated in control subjects when similar recording techniques were used. Thus, the ratio of the amplitude of subcortical waves obtained by the bipolar technique to that of waves derived from the scalp by either the mono- or bipolar technique varied as 1 : 2 to 1 : 3. In but one case, that of L.D., the ratio was as 1 : 1 (Fig. 3).

The amplitude of the waves derived from bipolar subcortical leads appeared to vary with the quantity of tissue between pick-up electrodes. Thus, the amplitude of electro-encephalograms recorded from between adjacent rings exhibited a central tendency of 5–30 μv, while that from between rings separated by an intermediate ring exhibited a central tendency of 20–35 μv. All these data closely resembled those demonstrable in control subjects and suggested that the recorded differences in amplitude *may be* less a

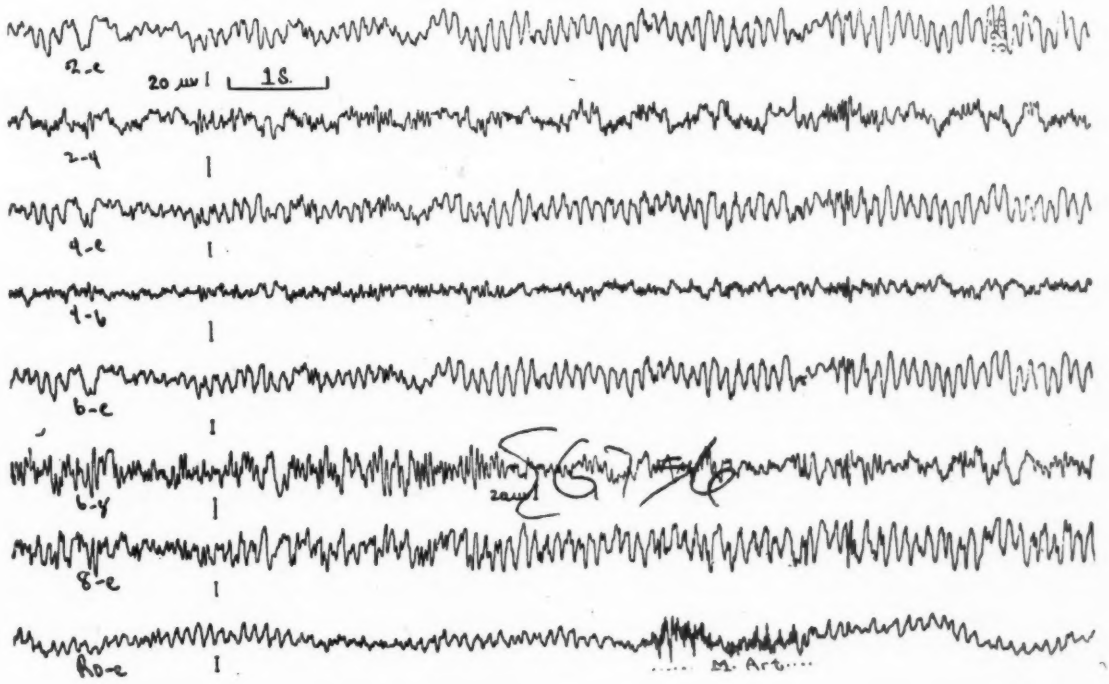

FIG. 3.—Electro-encephalograms of patient W.H., illustrating that the *frequency* of waves derived by bipolar technique from pick-up leads located in the region of the corpus striatum (2–4, 4–6, and 6–8) is higher than that of waves derived by monopolar technique ; (*a*) from leads in the region of the corpus striatum connected to the ear as reference electrode (2–e, 4–e, 6–e, 8–e) ; and (*b*) from scalp lead(s) similarly connected (RO–e). This record also illustrates that the *amplitude* of waves derived by the bipolar technique from leads in the striatal region is perceptibly less than that of waves derived by the monopolar technique from the striatal leads and by the mono- and bipolar techniques from the scalp leads. M.Art=muscle artefact.

function of the electrophysiologic dynamics of the tissues under inquiry than of the recording techniques employed. The issues cannot be resolved within the scope of this paper. The necessity for further study of the matter is indicated.

Temporal Relationships and Variations in Wave Form.—In general, the frequency and amplitude of waves derived from subcortical leads connected to the ear as reference electrode corresponded much more closely to the wave phenomena derived from mono- and bipolar scalp leads than to those derived from bipolar subcortical leads. Indeed, they were scarcely distinguishable from those obtained from the scalp leads. The non-correspondence which actually exists between the (mono-polar)

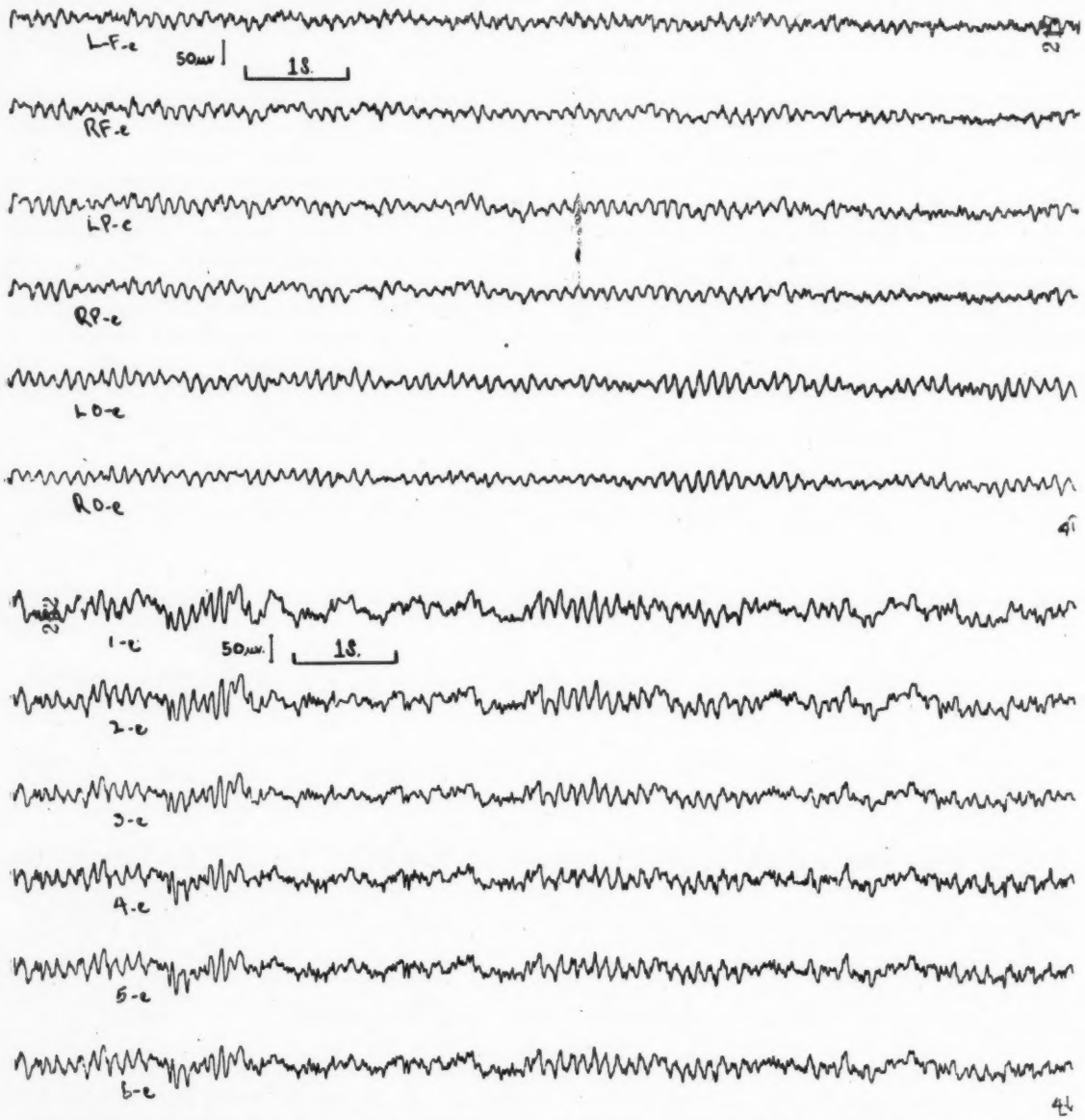

FIG. 4.—Electro-encephalograms of patient W.H., recorded by the monopolar technique; (*a*) from scalp leads to ear electrode (LF–e, RF–e, LP–e, RP–e, LO–e, and RO–e); and (*b*) from leads in the striatal region to ear (1–e, 2–e, 3–e, 4–e, 5–e, and 6–e). The close similarity in frequency and amplitude of the waves obtained from both sources is apparent from inspection. Although not illustrated here, waves derived by the bipolar technique from scalp leads closely resemble in frequency and amplitude all the recordings shown above.

sub-cortical electrograms and those derived from the scalp leads can best be demonstrated in consideration of their temporal relationships and variations in wave form (Fig. 4).

Two inferences appear warranted by these observations. The first is that waves derived from subcortical structures connected to the ears as reference electrode appear to reflect to a far greater degree the activity of cerebral tissues *between* the subcortical structure in which the ring-type electrode is located and the ears than they do the activity of the subcortical structure itself. This formulation is generally supported by all subcortical records obtained from both the experimental and control

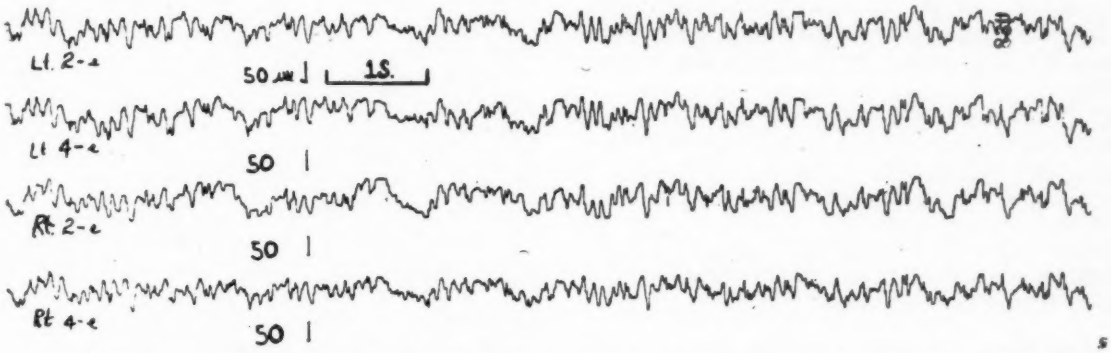

FIG. 5.—Electro-encephalograms of patient C.H., illustrating simultaneous monopolar recordings of electrical activity from the left (Lt 2–e and Lt 4–e) and right (Rt 2–e and Rt 4–e) neostriatal regions. These " twin " recordings from corresponding structures of the opposite sides are highly similar in frequency, amplitude, form, and polarity. The observation supports the view that monopolar recordings employing the ear as reference electrode reflect the activity of the adjacent temporal cortex to a greater degree than they do that of the striatal structures in which the ring-type electrode is located.

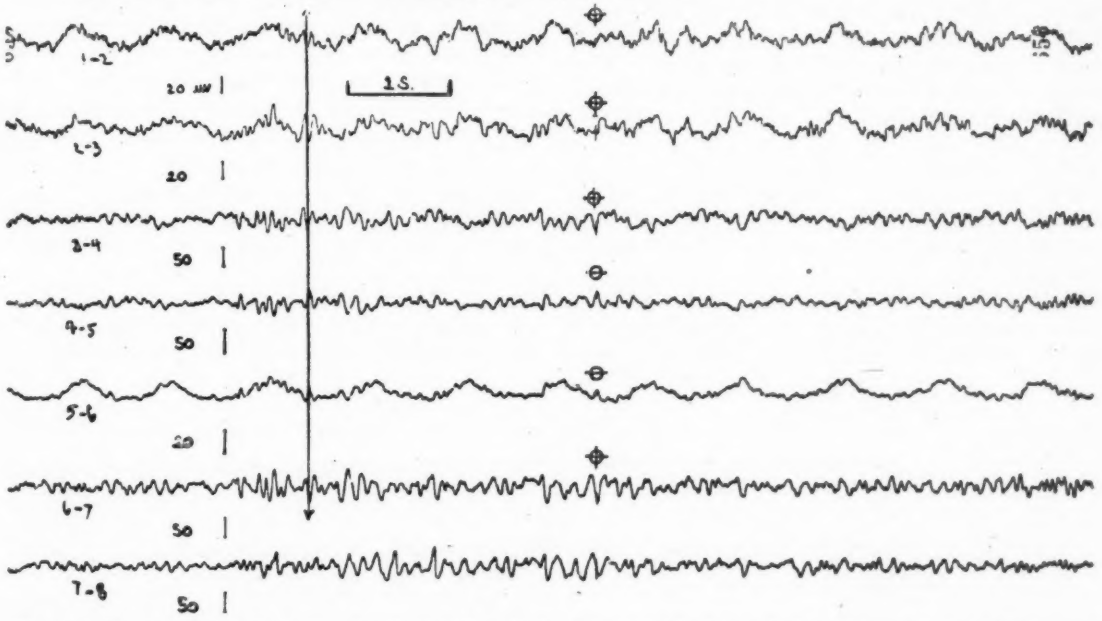

FIG. 6.—Electro-encephalograms of patient L.P., obtained by the bipolar technique from the neostriatum and neighbouring structures (compare with Fig. 1). The recordings demonstrate that waves derived from a circumscribed region, in this case the superior half of the head of the caudate nucleus (4–5 and 5–6), exhibit an electrical sign opposite that of waves from neighbouring tissues. Such a circumscribed region appears to act as a relatively constant source of electrical discharge and to impose upon circumferential tissues a reciprocal polarity.

⊖ = electronegativity ; ⊕ = electropositivity.

groups, but is particularly well illustrated in tracings simultaneously obtained from the right and left caudate nucleus of patient C.H. (Fig. 5). It will be noted that the electro-encephalograms thus obtained appear to be almost identical with one another. Evidently the frequency and amplitude of waves derived from tissues immediately surrounding the subcortical electrodes may be considerably " masked " by the electrical activity of cerebral tissues interposed between the deep-lying structures and the ear, notably the cortex of the temporal lobe.

The second inference that may be drawn is that an autochthonous electrical activity appears to be generated by the corpus striatum as well as by the cortex and that each of these foci of activity tends to exert electrical potential effects upon its own neighbourhood. There is no evidence at hand to indicate that under ordinary physiological conditions the one may be " submerged " by the other.

Fast Waves.—As in the control subjects, short-lived bursts of moderately fast (13–20 per second) waves characterized by a low-to-average voltage interrupted at irregular intervals the slower frequency phenomena generally prevailing in the subcortical leads. Such bursts were observed in electro-encephalograms derived from all subcortical leads in all subjects. With rare exceptions, their duration was less than one-half second and in no case was it found to exceed one second (Hayne and others, to be published).

Sites Explored.—No consistent differences in respect to frequency, amplitude and wave-form could be demonstrated among the several subcortical nuclei and neural tracts explored by the technique here employed. By and large, the recordings from the globus pallidus, putamen, head of the caudate nucleus, anterior limb of the internal capsule, subcallosal bundle, etc., displayed non-disparate electrical characteristics, as determined by analysis of their frequency, amplitude, and wave-form.

Reciprocal Polarity.—Analysis of the polarity of waves derived from the several subcortical structures suggested that a relatively constant " source " (or sources) of electrical discharge exists within circumscribed portions of the neostriatum. Such a " source " appeared to impose upon circumferential tissues a reciprocal polarity (Fig. 6).

In addition, the phenomena of (*a*) slight " shift of the discharging focus " and (*b*) " fluctuation of polarity " of the neighbouring tissues previously encountered in the control group had their counterparts in the experimental group. This observation accords with that of Adrian and Yamagiwa (1935) and Adrian (1936) in their delineation of the source of the occipital alpha rhythm. The latter " focus," like the foci demonstrated in the present study, appeared to be slightly variable, expanding, contracting, and wandering to and fro within a narrowly defined range.

" Fast Runs " in Parkinsonism.—In the bipolar subcortical tracings of five of the Parkinsonian cases (E.G., C.H., A.L., W.H., and W.B.) " fast runs " were frequently observed. These exhibited a wave frequency of 17–23 per second and a duration of from two to six seconds. Their amplitude was generally of the same magnitude as that of the prevailing (" dominant ") waves of the electrogram under examination (Fig. 7). An attempt to discover a correlation between the presence or absence of these fast runs and the degree of tremor and rigidity exhibited by the patient (see Table) was unsuccessful. The non-appearance of fast runs in the remaining five cases of the Parkinsonian group would seem to warrant the conviction that such runs do *not* constitute a uniformly demonstrable characteristic of the subcortical electrical potentials in Parkinsonism.

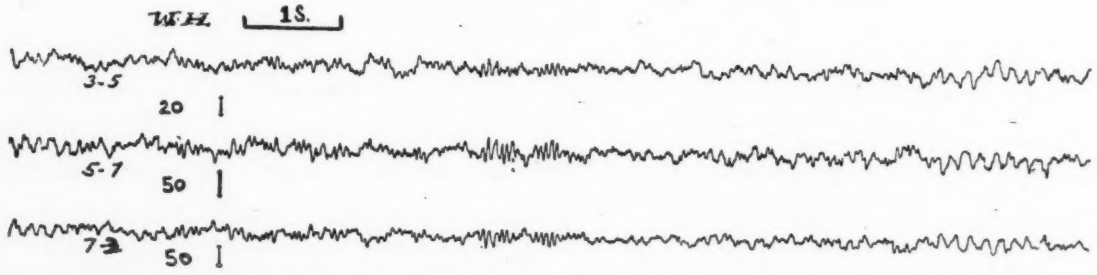

FIG. 7.—Electro-encephalograms from the striatal region of patient W.H., illustrating a " fast run " of 19-per-second waves having a duration of approximately 6 seconds and an amplitude approximately equal to that of the generally prevailing waves. The latter may be seen at the right and left extremes of the recordings. Such fast runs occurred irregularly in five of the ten Parkinsonian cases of this series. None of the control cases exhibited runs of this character.

A tenable explanation of these findings does not appear capable of formulation at present.

Slow Waves in One Patient.—In one Parkinsonian patient, W.B., the most conspicuous feature of the bipolar subcortical tracings was a slow (5½ per second) wave frequency of average amplitude. This phenomenon was apparent only in those waves derived from the tissues of a well circumscribed portion of the caudate nucleus (Fig. 8). The concomitantly-recorded electromyograms in this patient exhibited from time to time abnormal rhythmic oscillations, the rate of which (4 per second) was perceptibly slower than that of the electrocaudatograms (5½ per second). It appears unlikely, therefore, that the motor impulses delivered to the muscles were mediated in any *direct* fashion by electrical impulses from the caudate nucleus. Further evidence of the *lack* of correlation in this patient between the electrical activity of the caudate nucleus and that of the contralateral somatic muscles arose from the observation that the *electrocaudatographic recordings were unaltered by the appearance and disappearance of abnormal electromyographic oscillations* and from the further observation that *significant alterations of the electrocaudatograms corresponding to the appearance and disappearance of clinically observable tremors were not demonstrable.*

Correlation with Clinical Findings.—No correlation was apparent between the frequency, amplitude, and form of waves derived from the scalp and subcortical electrodes on the one hand and the clinically estimated degree of tremor and/or rigidity manifest in the patients suffering from Parkinsonism on the other (see Table). Nor was any correlation demonstrable when the electromyograms obtained from the affected limbs of these patients were compared with simultaneously-recorded scalp and subcortical electrical potentials (Fig. 9).

Hemiballismus.—The electrograms obtained from the single case of hemiballismus in the present series appeared to be similar in all respects to those obtained from subjects of the control series. This again was an unexpected finding.

Discussion

Impressed with the generally disappointing results of conservative therapeutic measures in the

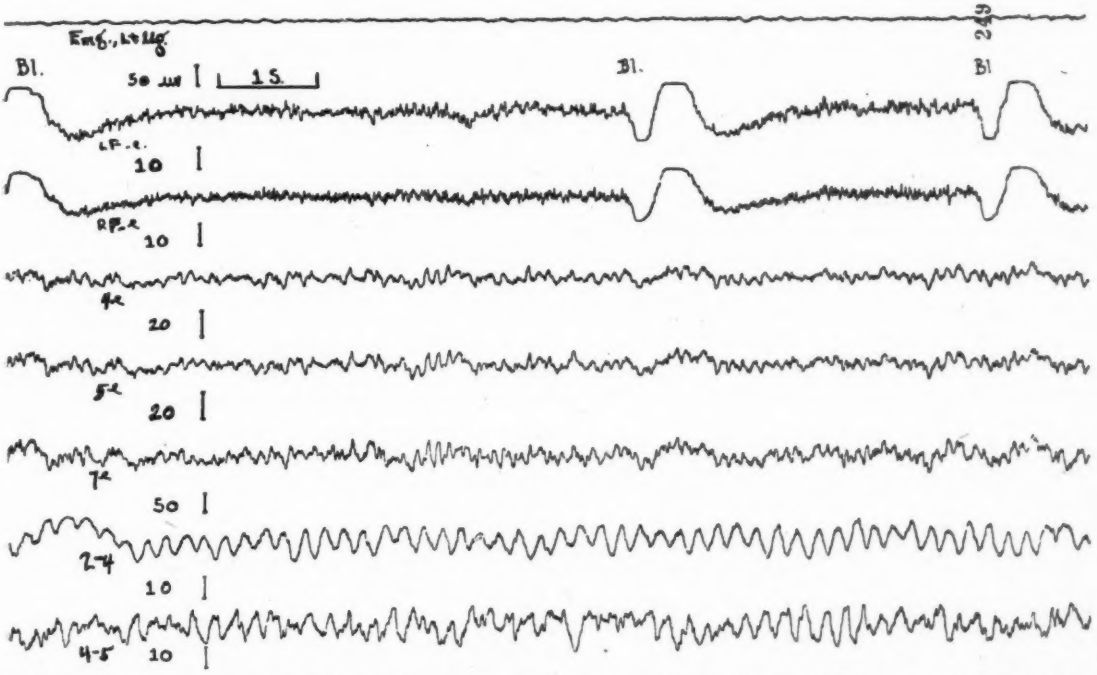

FIG. 8.—Electromyogram (Emg., left leg) and concomitantly recorded electro-encephalograms and electrostriatograms of patient W.B., illustrating (2–4 and 4–5) the slow (5½ per second) frequency of prevailing waves derived from the right caudate nucleus. The wave rate in this subject was unique among the subjects of the experimental and control groups. During the recording of the brain waves here illustrated, the electromyogram was quiescent, the tremors in the left lower limb having 'spontaneously' subsided for the moment (Compare with Fig. 9). Bl=eyeblink. Muscle artefacts may be seen imposed upon the electro-encephalograms from leads LF–e and RF–e.

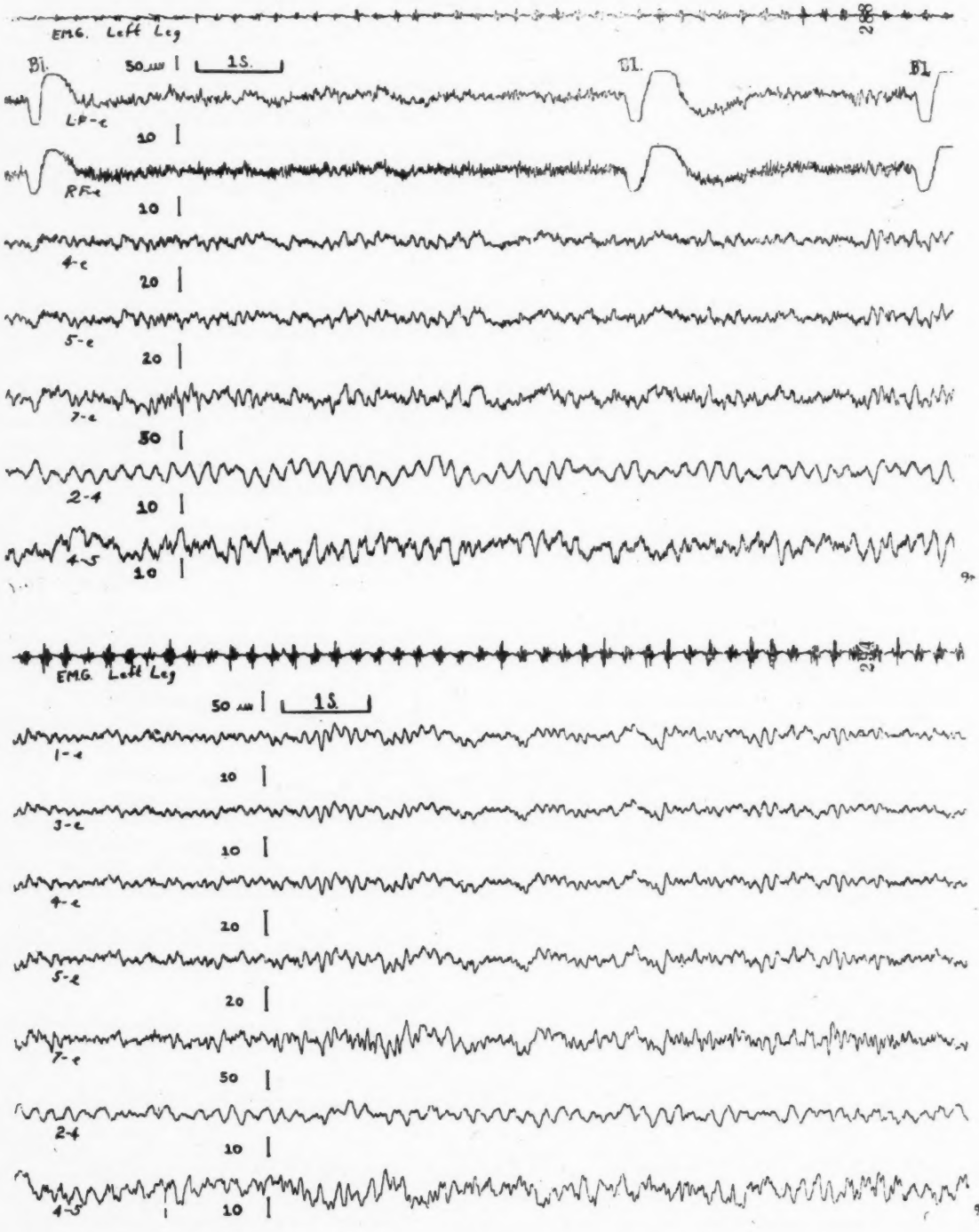

FIG. 9.—Electromyogram (Emg., left leg) and simultaneously recorded electro-encephaiograms and electro-striatograms of patient W.B., illustrating the gradual reappearance of tremors (upper record) and full-blown presence of tremors (lower record). The frequency of the electrotremograms is consistently 4 per second. The electrostriatograms recorded by mono- and bipolar methods are apparently unaltered, irrespective of the spontaneous ebb and flow of tremors (compare with Fig. 8).

treatment of Parkinsonism, several investigators* endeavoured during the years 1930–42 to devise central neurosurgical procedures which might ameliorate tremors, rigidity, and the related incapacitating symptoms of the disorder. The first of these attempts, that carried out by Puusepp (1930) and repeated by Rizzatti and Moreno (1936) consisted in surgical section of the column of Burdach in the cervical cord. This failed to achieve its purpose. Shortly afterward, Putnam (1938b), pursuing the attack upon spinal cord mechanisms, reported disappointment in section of the anterolateral funiculus at high cervical levels. Interruption of the crossed pyramidal tract, however, was followed for some months by substantial improvement (Putnam, 1938a, b, 1940a, b). In 1939, Bucy and Case reported their experience with a cerebral approach, extirpating portions of the motor and premotor cortices. Subsequently, the cortical attack was more intensively pursued by Bucy (1944), Putnam, White, and Klemme (1940). The evidence obtained by these workers appeared capable of general formulation somewhat as follows: the abolition of tremor requires the surgical destruction of the precentral cortical projections of the affected limb(s), notably, Brodmann's areas 4 and portions of 6-a. The inevitable consequence of the operation is a spastic paresis of the limb(s) with tendon hyperreflexia and enduring dyspraxia. Bucy's (1944, 1948) critical evaluations led him to assert that the procedure was warranted only in patients already severely disabled by Parkinsonism. He added that, in view of the functional deficits above enumerated, bilateral operation was not justifiable.

One of us (R.M.) experimented with extirpations and sections of several structures at the level of the basal ganglia. The findings encountered in the first twelve cases were reported upon in 1941 and 1942. This line of experiment has been resumed since the conclusion of the 1939–45 war, and the data will be reported in a later communication. The attack on the deep-lying structures has been further pursued by Browder (1948) in sectioning fibres of the anterior limb of the internal capsule back as far as the genu. The most recent procedure, carried out by Wyke (personal communication) in thirty-six cases, renews the attack at the cortical level. In Wyke's procedure a simple incision running parallel and just rostral to the suppressor strip (area 4-s) is made through the cortex and subcortical U-fibres, thus separating the more direct cortico-cortical connexions between areas 4 and 6 (McCulloch, 1944).

With regard to the several surgical procedures—pyramidal, cortical, subcortical, and basal ganglionic—referred to above, some highly encouraging results have been realized in some instances and disappointing results in others. The slowly-accumulating factual data has permitted the tentative formulation of pathophysiologic concepts (Bucy, 1944; Meyers, 1941) bearing upon the hyperkinetic disorders. These are at present in process of evaluation.

Of the several experiments carried out at the level of the basal ganglia, that of pallidofugal section appeared to be the most promising in the sense that, when effective, the patient's tremors were virtually abolished, his rigidity phenomena perceptibly diminished, and the various clinical disabilities consequent upon poverty of movement substantially improved. Highly important was the observation that the patient did not suffer further embarrassment of motor, co-ordinative, eupractic, and speech functions such as those frequently described as the sequelæ of cortical extirpations and interruptions of the crossed pyramidal tract at the cervical cord levels. Unfortunately, some failures were encountered with the pallidofugal procedure as with all other procedures. These failures necessarily called for speculation as to the underlying reasons. One obvious suggestion was that the operative procedure itself had not been performed with equal precision in each case. While evidence was not (and even now is not) such as to permit dismissal of this account, the operator felt that a fair standardization of procedure had been worked out in regard to pallidofugal section and that other theoretical accounts merited exploration. In 1941 an alternative notion was tentatively proposed (Meyers, 1941) which depended for its support upon two thought-provoking circumstances: (*a*) the highly contradictory character of apparently reliable histopathologic studies in Parkinsonian and non-Parkinsonian cases; and (*b*) the disparate results obtained in connexion with each of the various surgical procedures. In effect, this hypothesis suggested that Parkinsonism might profitably be regarded as a *clinical manifestation* rather than as a "disease entity" and that, from the *pathophysiologic* point of view, it might well turn out that multiple (as opposed to unit-factor) neural mechanisms subtend the disorder. It seemed reasonable to suppose that one or more of the postulated mechanisms might indeed be common to all cases, but that this circumstance in no way impelled the conviction that all mechanisms are identical in all cases presenting similar clinical findings. If, as hypothesized, the

* Browder, 1948; Bucy and Case, 1939; Bucy, 1944, 1948; Delmas-Marsalet and Van Bogaert, 1935; Foerster and Gagel, 1932; Klemme, 1940; Machanskij, 1935; Meyers, 1940, 1941, 1942a and b; Oldberg, 1938; Putnam, 1933, 1938a and b, 1940a and b; Puusepp, 1930; Rizzatti and Moreno, 1936.

neural loops functionally usurped in some cases differed from those usurped in others, the result obtained by a given operative procedure would clearly depend upon whether the usurped loop, as an integral part of the tremor-producing complex, had or had not been surgically interrupted.

If, then, the notion of pathophysiologically different kinds of Parkinsonism may tentatively be entertained, it manifestly becomes a matter of practical importance for the clinical investigator to decide *pre-operatively* whether a candidate is likely to derive benefit from surgery. And, assuming the answer to be in the affirmative, it becomes equally important for him to decide which of several possible operative procedures appears most applicable to the case in hand.

It was with the hope that some light might be thrown upon these matters that the present study was projected. The results unfortunately do not permit a resolution of the relevant issues. They do, however, appear to lend some support to the hypothesis that the subtending pathogenetic processes may indeed differ somewhat from case to case. This inference is suggested by (*a*) the peculiar " fast runs " encountered in five of the ten Parkinsonian subjects, (*b*) their absence in the remainder, and (*c*) the singularly slow frequency encountered in the electroneostriatogram of patient W.B. No comparable recordings were seen in the eleven control subjects. That such electrographic differences do exist is inescapable. Their clinical significance remains to be elucidated.

Summary

1. Electrograms were recorded from the neo- and paleostriata and their neighbourhood in ten cases of Parkinsonism and one of hemiballismus. The wave characteristics of frequency, amplitude, form, and polarity were compared with (*a*) the corresponding phenomena of concurrently-recorded electroencephalograms obtained from standard scalp leads and (*b*) electromyograms of the tremor-affected limbs. All data derived from the experimental group (here reported upon) were evaluated in view of data and interpretations derived from eleven control subjects (elsewhere reported upon). Twenty-one experiments were performed upon the experimental group and eleven upon the controls.

2. The frequency of waves derived by the bipolar technique from the several structures of the corpus striatum and neighbourhood varied from individual to individual and from time to time within each individual. The rate of electrograms recorded (by the bipolar method) exceeded that of electrograms derived from the scalp leads (by both the bipolar and monopolar methods) by one to several cycles per second. Similar observations were made among the control subjects.

Short-lived bursts of moderately fast frequency (13–20 per second), having a duration of 0·5–1·0 seconds and a low to average voltage interrupted at irregular intervals the slower frequency, higher amplitude waves generally predominating in recordings from leads placed in the corpus striatum. Such were observed in the electrostriatograms of all subjects in both the control and experimental groups.

3. The amplitude of electrostriatograms obtained by the bipolar technique varied from individual to individual and from time to time within each individual, approximating 14–25 μv. This was of smaller magnitude than that of electro-encephalograms concomitantly recorded by mono- and bipolar techniques from the standard scalp leads, the ratio being as 1 : 2 to 1 : 3.

Evidence at hand suggests that the differences in amplitude between electrostriatograms and electroencephalograms depends upon the smaller quantity of tissue between pick-up electrodes in the former (as compared with the latter), rather than upon the electrophysiologic properties of the cerebral tissues themselves. The findings relevant to amplitude were similar for both the control and experimental groups.

4. Whether electrograms were derived from scalp-ear or striatum-ear leads (that is, by the monopolar technique), the frequency and amplitude of the waves were very similar. This similitude probably arises from the proximity of active cortical tissue of the temporal lobe to the electrode attached to the ear. The non-correspondence which genuinely exists between the electrograms from the two mentioned sources was demonstrable in terms of their disparate temporal relationships and variations in wave form. The phenomena were obtained in the controls as well as in the experimental group.

5. Electrograms derived from the several deep-lying structures explored (for example, caudate nucleus, putamen, globus pallidus, subcallosal bundle, etc.) exhibited no features by which one structure might be distinguished from its fellows. This observation held among both the experimental and control subjects.

6. Analysis of the phenomena of wave polarity and reversal of electrical sign of the electrostriatograms strongly suggested that a relatively constant, circumscribed source(s) of electrical discharge obtains within the head of the corpus striatum and/or the putamen. Such a region was almost continuously possessed of an electrical sign opposite to that of the surrounding zones. Similar findings obtained among the control subjects.

7. The bipolar electro-encephalograms derived from the corpus striatum of four among the ten cases of Parkinsonism exhibited no features by which they could be distinguished from the comparable electro-encephalograms of control subjects. Of the six remaining cases, however, five exhibited "fast" runs (rate, 17–23 per second; duration, 2–6 seconds; and amplitude comparable to that of the prevailing waves of the record). Such runs frequently interrupted the slower-frequency phenomena generally characteristic of the subject's record. The sixth case, on the other hand, exhibited a singularly slow rate of dominant waves ($5\frac{1}{2}$ per second). The source of the latter appeared to be a well circumscribed region in the dorsal half of the caudate nucleus. The phenomena observed in these six cases had no counterpart among the control subjects. It was not possible to identify a consistent relationship between (*a*) the type of electrostriatogram derived from a given subject and (*b*) the kind and degree of clinical features of Parkinsonism exhibited by him.

8. No relation was apparent between (*a*) the electrical activity of the corpus striatum and neighbouring structures and (*b*) the presence or absence of electromyographic activity and clinically observable alternating tremors. Moreover, when electromyograms corresponding to tremor activity were recorded, their frequencies (4–5 per second) did not correspond to those of the concomitantly-recorded electrostriatograms and electro-encephalograms.

9. The electro-encephalograms obtained from the one case of hemiballismus in the experimental group did not differ greatly from those of eleven control subjects.

10. The findings lend support to the hypothesis that, from the pathophysiologic point of view, Parkinsonism may differ from case to case in regard to the neural loops usurped. A multiordinal concept of the neural mechanisms involved in the production of tremors and rigidity is suggested, in contradistinction to a unit-factor process (for example, "disease" of the substantia nigra) such as has traditionally been sought in histopathologic terms.

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DURATION AND FORM OF ACTION POTENTIAL IN THE NORMAL HUMAN MUSCLE

BY

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Introduction

The insight obtained into changes in the electrical activity of the muscle in certain neuromuscular disorders and the refinement of their electromyographic diagnosis have made it necesssry to determine more precisely the variations in the form and duration of the action potentials in the normal muscle.

The form of the action potential recorded with a standard electrode (concentric or monopolar needles) is generally stated to be a mono-, bi-, or triphasic wave. Polyphasic potentials are occasionally observed, (Denslow and Hassett, 1943 ; Weddell and others, 1944). Their relative frequency, however, has not been determined.

In the normal muscle the duration of the single motor unit action potential, recorded with concentric needle electrodes and adequate measuring instruments, was found by Buchthal and Clemmesen (1941) to be about 7 to 14 msecs. The duration of the first rapid phase of the action potential was subjected to statistical analysis and found to be 4·64 msecs., with a standard deviation of 7·4 per cent. The measurements were made from photographic tracings of " lying waves," with a camera transporting the paper at high speed. Owing to the large consumption of paper, however, this method is far too expensive for use in ordinary clinical work. Similar methods were adopted by Weddell and others, (1944), who state that the duration of the action potential in the average limb is 5 to 10 msecs. The corresponding figures given by Jasper (1946) are 5 to 8 msecs., and by Kugelberg (1947), for the majority of the potentials, 4 to 10 msecs. These figures include potentials of less duration than those first mentioned. Snodgrass and Sperry (1941) report the occurrence of still shorter potentials, with a duration of 1 to 3 msecs.

It may be seen from the above summary that exact figures for the normal variations in the duration of the action potentials are lacking. This applies not only to the distribution of the duration in the same muscle, but also as to whether there are any differences in this respect between different muscles and different persons. Nor has any clinically serviceable method for the determination of the duration been tested, nor the effect of the commonly used electrode types on the duration investigated. These are the chief problems discussed in the present paper.

Technique and Method

As a standard electrode, a coaxial needle electrode (platinum wire, 0·20 mm. in diameter, insulated by a glass capillary tube from the cannula of stainless steel with an outer diameter of 0·5 mm.) was employed. The inner core was well centred in the tip of the cannula, care being taken that its end lay in the same plane as the cannula or slightly beyond it. The inclination of the tip was 45 degrees.

A needle with the same dimensions as stated above, but with two platinum wires 0·10 mm. in inside diameter, and with the needle grounded, was also tested. A third type of electrode employed consisted of fine sewing needles (No. 8), insulated by covering with three coats of plastic baking enamel. Though the tip, owing to the surface tension, remains uncoated, it was gently rubbed once against a fine-grained whetstone.

The action potentials were led off to a one-channel balanced push-pull amplifier (time constant 0·3 second) connected to one beam of the cathode-ray tube, the other beam being connected to an oscillator for time recording in milliseconds.

In order to obtain detailed pictures of single action potentials, the sweep was caused to carry the ray horizontally over the screen about three times a second. A camera, taking 120 metres of film paper, simultaneously carried the film vertically in front of the tube, so as to obtain a series of pictures of the several sweeps above one another across the strip of film. The sweep velocity was adjusted each time so as to permit determination on the record of a duration of 0·5 to 5 msecs., within an accuracy of about $\pm$0·25 msec., and for a duration of 5 to 10 msecs. within an accuracy of $\pm$0·5 msec.

The determinations of the duration were made only on potentials with a well-defined beginning and end. The entire duration was measured. The amplification was 100 microvolts, corresponding to 2 mm. on the record. It was necessary for the base line to be stable in order to enable the duration to be determined. For this reason only the three, or exceptionally four, first spikes recruited according as the voluntary contraction increases, have been taken as a basis for the determinations recorded in this paper. On intense contraction the base line will be disturbed owing to distant activity from muscle masses surrounding the needle. Moreover, according as an increasing number of units are recruited, they will often interfere with one another, so that it will be increasingly difficult to distinguish the individual potential. A criterion indicating that we have been concerned with a single functional unit, and not with a temporary coalescence of two or more, is that the unit in question had recurred on the record at least three times with identical form, duration, and amplitude.

Results

Influence of Electrode Type.—In the application of clinical electromyography to neuromuscular disorders, the electrode, without much probing, should give a relatively undistorted single unit response, at any rate to weak contraction. Furthermore, the pain felt on insertion of the electrode should be so slight that the operator can venture to examine each muscle at several points, or to examine several different muscles. The electrode, once placed in the muscle, should cause only slight discomfort and should not interfere with the patient's voluntary contraction. To minimize the pain a concentric needle electrode should not exceed 0·5 to 0·6 mm. in diameter.

The following electrode types are used in human electromyography :

1. The concentric needle electrode of Adrian and Bronk (1929).

2. Fine sewing needles coated except on the tip. They have been used monopolarly with a reference electrode on the surrounding skin, or bipolarly, for example, by Gilson and Mills (1941), Cuthbert and Denslow (1945), and Jasper (1946).

3. Two fine insulated wires inside a hypodermic needle, with the needle grounded (Adrian and Bronk, 1929 ; Lindsley, 1935). This electrode, being highly selective, has been used in frequency studies in order to follow single action potentials even under strong contraction.

For routine work, types 1, and 2 used monopolarly, have given satisfactory results. In the larger muscles it is somewhat easier to obtain single motor unit action potentials with the lacquered sewing needles than with the concentric electrodes. Little difference in this respect is found in examining smaller muscles, such as the intrinsic muscles of the hands and feet. The concentric double electrode, on the other hand, takes up activity from a very restricted area. One will, therefore, have to search more in order to find single action potentials. When they are discovered, it is difficult to record them for more than a few moments. In fact a minimal displacement of the needle will suffice to bring the action potentials beyond the picking-up range of the electrode. For this reason the concentric double electrode is not well suited for ordinary electromyography.

Duration determinations with the three different types of electrode (100 action potentials examined at the first dorsal interosseous muscle in ten individuals) yielded the following results :

Type 1.	Mean $7{\cdot}34 \pm 0{\cdot}21$.	Standard deviation	2·1
Type 2.	„ $7{\cdot}29 \pm 0{\cdot}24$.	„ „	2·4
Type 3.	„ $2{\cdot}01 \pm 0{\cdot}10$.	„ „	1·0

There is thus no statistically significant difference between the duration measured with types 1 and 2. Type 3, on the other hand, shows considerably lower figures for the duration.

The amplitudes of the action potentials are, on an average, smallest with type 3, and largest with type 2. The results obtained with types 1 and 2 in this respect are not comparable. No difference in the form of the action potentials has been observed when different electrodes were used.

Form of Action Potentials.—The most common types are bi- or triphasic waves (Fig. 1B and C). Monophasic waves are less common (Fig. 1A). They often have a poorly defined beginning and termination. Deviations from the more symmetrical appearance of the wave forms seen in A-C frequently occur (D-F). This, of course, is to be expected when recording electrical activity spreading in a volume conductor from such a variable structure as the " motor unit."

As has been noticed by Buchthal and Clemmesen (1941), the action potentials are often slightly split up (Fig. 1G). Such potentials, when recorded at a lower speed, have a notch on the spike. If at one or more points on the potentials this disintegration goes further so that it extends over the base line (Fig. 1H-J), they have quite arbitrarily been regarded as polycyclic. The latter are rare in the average limb muscle, occurring to the extent of from only 2 to 4 per cent. among six hundred counted potentials in the first interosseous muscle, and among three hundred in the biceps brachii. As noted by Jasper (1946), polyphasic potentials are commoner in the facial muscles (Fig. 1H).

Duration of Action Potentials.—Duration determinations were made in thirty cases, ten women and twenty men, between the ages of twenty and forty-

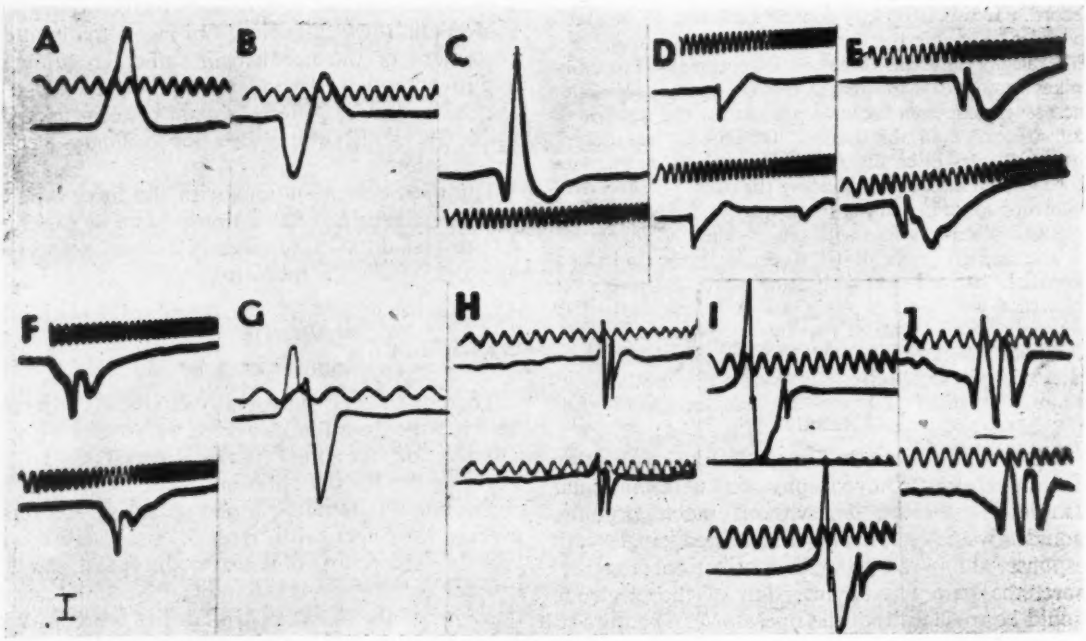

FIG. 1.—Examples of different forms of action potentials in the normal human muscle. G and H are from the facial, the remainder from the biceps and interosseous muscles. Calibration 100 microvolts. Time 1/1000 sec.

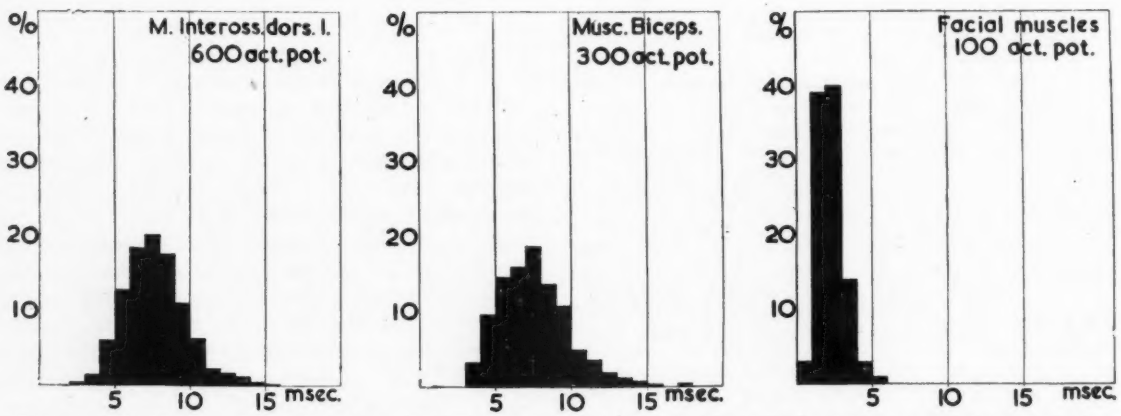

FIG. 2.—Distribution of the durations of action potentials in dorsal interosseous, biceps, and facial muscles.

two years. In each person the duration was computed for twenty action potentials in the first interosseous muscle and ten in the biceps brachii, while a total of a hundred observations were made in the facial muscles. The distribution of the duration of the potentials in the respective muscles is shown in Fig. 2. The extreme limits are between 2 and 16 msecs. for the first interosseous muscle, 3 and 18 for the biceps, and 0.8 and 6 for the facial muscle. The much shorter value for the facial muscle is in accordance with the observations of Feinstein (1946).

The differences in the action potentials have been analysed with Fisher's method (1941) in regard to the variation between different persons as well as in each individual person. This analysis of variation shows no significant differences between the different individuals.

The entire number of observations may thus be regarded as a homogeneous unit. The normal limits for the mean value of a given number (n) of determined potential-durations can thus be computed by dividing the standard deviation for the entire series of observations by the square root of n.

The means of the total number of determinations in the different muscles are :

First interosseous muscle	$7{\cdot}68 \pm 0{\cdot}07$.	Standard deviation 2·07
Biceps brachii	$7{\cdot}56 \pm 0{\cdot}14$.	„ „ 2·37
Facial muscle	$2{\cdot}28 \pm 0{\cdot}03$.	„ „ 0·30

The standard deviation of the mean for ten and twenty measured potentials and the range of variation for the corresponding means, computed according to 2.5σ on either side of the mean, will consequently be :

First interosseous muscle	$n=10$	0·65.	Range 6·05—9·31
	$n=20$	0·45	„ 6·53—8·83
Biceps brachii	$n=10$	0·75.	„ 5·78—9·34
	$n=20$	0·53.	„ 6·23—8·89

The normal values obtained for the potential-durations in experimental subjects aged 20 to 42 years—a group within which no noteworthy individual differences in respect of sex and age could be ascertained—as compared with those in persons of advanced age, are somewhat shorter. The means of twenty measured potentials in the first interosseous muscle of 5 men aged from 69 to 79 years were 8·5, 8·9, 9·1, 10·9, and 11·3. The three last mentioned values show a significant increase relatively to the normal values in the preceding group. The value 8·9 is statistically probably increased.

Discussion

The method adopted for computing the duration of the action potentials is doubtless liable to give somewhat too short durations, as slow changes in a potential of small amplitude are apt to be masked by slight irregularities on the base line, or may not be observed with the amplification used. On the other hand, if the method is carried out uniformly as regards amplification and recording procedure, it has proved to be quite serviceable in clinical practice. Deviations from normal conditions have been distinctly observed in different pathological material (Kugelberg, 1949). In clinical routine, however, exact measurements from tracings are seldom necessary, but can be replaced with observation of the activity on a large screen with a time scale, or with Bauwens' (1948) ingeniously designed apparatus.

It is evident that the electrode type used affects the recorded duration and amplitude of the action potentials. As regards the duration, the results with the concentric needle electrodes of the same dimensions or thicker than those used here are comparable with those obtained with the monopolar needle. This, however, does not apply to the amplitude. We have also the impression that the concentric needle electrodes should not be too obliquely cut. Some measurements were made. Greatly bevelled electrodes seemed often to produce distorted action potentials of somewhat shorter duration than our standard electrodes. Moreover, they were liable to cause contact defects at the tip, and on some occasions to cut off all action potentials to a few milliseconds.

The very short values obtained with the double electrode may be explained not only by its other physical properties as compared with that of the standard types, but also by the great selectivity of the electrode itself. If the selectivity is sufficiently marked, the electrode will take up activity from a smaller part of the motor unit than a less selective electrode. This because the motor unit has a large distribution, not only lengthwise along the muscle (Cooper, 1929), but also in width, which is due to the fact that the muscle fibres composing the motor unit do not form a close bundle, but are scattered and intermingled with muscle fibres from other units (Wohlfahrt and Wohlfart, 1935 ; Brodal and Refsum, 1942).

It is evident that, in order to obtain comparable results whenever quantitative measurements are made in regard to duration and amplitude, as well as the number of action potentials recruited in the picking-up range of the electrode, the electrode type must be standardized.

The mean of the duration of ten or twenty action potentials shows (within the error of the method) very small differences from case to case among the above-mentioned normal persons between the ages of 20 and 42 years The duration of the action potentials is evidently a factor in the electromyogram that is well suited for quantitative determinations.

The biceps and interosseous muscles were selected as standard muscles for the purpose of this investigation in view of the fact that they are often subject to pathological changes in different diseases. Moreover, they can be easily examined. The very short values of the facial muscles indicate that the number of muscle fibres in the motor units of these muscles are small as compared with those within the muscles of the extremities and trunk.

A slight prolongation of the duration of the potentials was found at advanced ages. This change may be accounted for on the supposition that the duration of the action potentials had actually become longer. But it may also be merely apparent, being due to the elimination of the action potentials first recruited by the voluntary contraction. In such circumstances the measurements will be made on potentials with a higher threshold for voluntary activation, for the duration of which no normal values are at present available. Seeing that their amplitudes are considerably larger it is plausible to suppose that their durations may likewise be increased. It should be borne in mind that the normal values recorded in this paper refer to the motor units first recruited and which are connected to the nerve fibres with the lowest threshold for a slowly rising current (Kugelberg and Skoglund, 1946), indicating a large fibre diameter. Any process that, more or less selectively, destroys the fibres with the largest calibres will cause the duration determinations to be made on another group of action potentials than that on which the normal values are based. At advanced ages, as shown by Rexed (1944), the calibre spectrum of the dorsal and ventral root fibres shows a tendency to shift to the shorter side, owing to destruction of fibres mainly of large size.

Summary

1. Duration and amplitude of action potentials, as well as the number of recruited spikes in the electromyogram at maximal voluntary contraction, varies with the type of electrode used. To obtain comparable results the type of electrode must be standardized.

2. Some typical forms of action potentials are demonstrated. Polycyclic potentials occur in from 2 to 4 per cent. of the potentials in the biceps and interosseous muscles.

3. The duration of action potentials in the interosseous, biceps, and facial muscles in adults are statistically defined. With old age the duration is somewhat lengthened. Its cause is discussed.

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ELECTROMYOGRAPHY IN MUSCULAR DYSTROPHIES

DIFFERENTIATION BETWEEN DYSTROPHIES AND CHRONIC LOWER MOTOR NEURONE LESIONS

BY

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Introduction

In a recent issue of this journal (Kugelberg, 1947) the electrical activity of voluntary muscle was studied in various forms of muscular dystrophies and lesions of the lower motor neurone, with special regard to differentiation between them.

The electromyographic differential diagnosis between muscular dystrophies and atrophies was formerly based on the finding of Buchthal and Clemmesen (1941) that " single discharge " on maximal voluntary contraction was not observed in genuine myopathy, even in extremely severe cases. In neurogenic lesions, on the other hand, "single discharge " occurred even when the weakness was moderate.

The observation that a decrease in the number of spikes relatively to the muscular power exerted occurs much later in myopathies than in neurogenic lesions, was confirmed (Kugelberg, 1947). " Single discharge," however, was regularly observed even in myopathy, provided that the changes were sufficiently advanced. As no diminution in the number of spikes could be observed in mild cases of myogenic and neurogenic paresis, and as both may show " single discharge " when the weakness is extreme, the need of more specific signs of myopathy in the electromyogram became acute. Moreover, it is always unsatisfactory in intermediate degrees of weakness to diagnose the case as myopathy, on the ground that " nothing abnormal can be seen."

A positive symptom of myopathy was found, however, in the occurrence of action potentials of short duration (1 to 2 msecs.). They increase in relative number according as the weakness advances. As regards the material examined, the action potentials observed in the myogenic " single discharge " were invariably of this type. Thus a reliable differential diagnosis could be made in all but the mildest degrees of weakness, being more and more easily determinable as the weakness advanced.

It had been assumed that the characteristic rapid spikes in myopathies were produced by a shortening of the duration of the normal spikes ; this and the other changes being accounted for by a process which, more or less diffusely, gradually reduces the number of fibres composing the different motor units until at length they are completely put out of action.

To test this view, and further to establish the electromyographic picture in muscular dystrophies as well as to differentiate it from diseases of the lower motor neurone, changes in the form of the action potentials have been studied, and measurements of their duration have been made, as reported in this paper. The significance of such measurements can be evaluated quantitatively, as the form and duration of the action potentials in the normal muscle have now been defined (Petersén and Kugelberg, 1949) with the same technique as adopted in the present investigation.

Methods

Concentric needle electrodes were used (platinum wire 0·20 mm. in diameter insulated from a cannula having an outer diameter of 0·5 mm.). The recording procedure has been previously described (Kugelberg, 1947 ; Petersén and Kugelberg, 1949).

The muscles were examined for (1) the occurrence of spontaneous activity and intensification or lessening of the response on mechanical stimulation by the exploring needle electrode ; (2) the form, duration, and in some cases amplitude of the action potentials ; and (3) the number of recruited spikes within the picking-up range of the electrode on maximal voluntary contraction compared with the strength of the muscle.

Results

Electrical Activity in Muscular Dystrophies : Proximal Forms.—Seven adults (Cases 1 to 7) and one child (No. 8) with the common proximal forms of muscular dystrophy were examined. In the first place the biceps muscle, in regard to which variations in the duration of the action potentials had previously been determined in normal cases, was examined. Different degrees of weakness were represented : (a) maximal atrophy (Case 1) or pseudohypertrophy (Case 2) with no palpable or clinically observable response to attempts at voluntary contraction ; (b) severe atrophy and the bare capacity to flex the joint against gravity (Case 3) ; (c) severe atrophy and capacity to flex the joint against gravity plus slight active resistance (Cases 4 and 5) ; and (d) no atrophy, and slight but definite paresis (Cases 6 to 8).

TABLE I

PROXIMAL DYSTROPHY
(Biceps Brachii)

Case	Action potentials counted	Mean	Polycyclic percentage	Duration less than 3 msecs. percentage
1	10	2·4	—	80
2	25	3·3	16	40
3	50	2·3	32	80
4	30	2·8	7	70
5	25	2·7	16	68
6	50	3·9	20	44
7	20	3·9	10	25
Normal values	10	5·8–9·3	4	approx. 1

1. Spontaneous fibrillation did not occur in any case.*

*Particulars of the mechanical response on stimulation by exploring electrode will be published in a later article, and compared with the response in the normal and denervated muscle.

2, The distribution of the duration is recorded in Cases 1 to 7 (Fig. 1 and Table I). It shows a considerable shift towards the short side relatively to the normal biceps. As expected, action potentials with a normal duration were most numerous where the biceps was clinically least affected (Cases 6 and 7). In other cases there was no strict correspondence between the reduction of the average duration and the degree of weakness. It is also evident that action potentials of normal duration may occur even in advanced stages of the disease. Moreover, in Case 2, with clinical paralysis of the biceps, there were no potentials with a maximal reduction to 1 or 2 msecs. The average duration, however, as in the other cases, was statistically significant, well below the normal limits. The absence of 1 to 2-msec. spikes in muscles with clinically advanced changes is rare, not being observed in any other case. In the same patient they were numerous in other muscles examined.

Owing to the occurrence of action potentials of relatively long duration (4 to 5 msecs.) even in cases of advanced changes, " single discharge," consisting

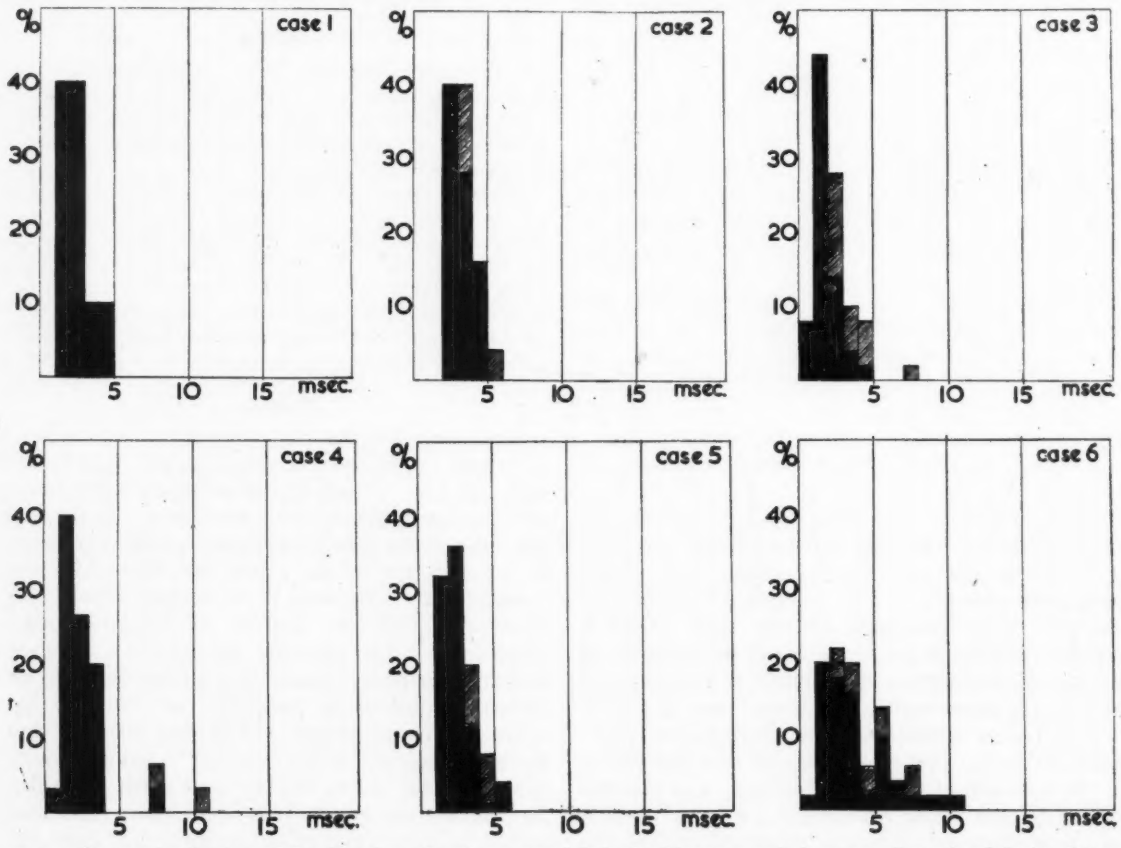

FIG. 1.—The distribution of the duration of action potentials in the biceps muscle in cases of proximal dystrophy. The portions shaded with oblique lines indicate polycyclic potentials.

of normal potentials, may be obtained exceptionally at certain positions of the needle. In such cases it becomes a statistical problem to work out a pathological reduction of the duration of the potentials, as it becomes necessary to sample action potentials from several different needle positions.

Some polycyclic action potentials in muscular dystrophy were observed in one case by Bowden and Gutmann (1946). They also occur normally, however (Denslow and Hassett, 1943 ; Weddell and others, 1944), to the extent of from 2 to 4 per cent. in the biceps muscle (Petersén and Kugelberg, 1949). An increase in their frequency, or differences in their form and duration, will therefore have to be shown if any significance is to be attached to the findings in dystrophies. Normally the duration is rather long, 8 to 12 msecs.

The frequency of polycyclic action potentials was significantly increased in four out of seven cases (Table I). In Case 1 none was discovered. Here the muscle was very severely affected. Only ten different potentials could be found, most of which were of such short duration that no further disintegration could be expected. As shown by the histograms, the duration is mostly below the average for that of the normal action potential, down to 3 msecs.

Some typical polycylic potentials (from Case 6) are shown (Fig. 3). Most of them consist of components of very short duration. They are arranged (C–E) so as to show tentatively how the normal action potential B is broken up, and finally, through the rapid action potential G, is reduced to a potential H, resembling the fibrillary spike (duration about 1 msec. and amplitude about 150 microvolts). (See the discussion.)

3. Patients with extreme paresis (Cases 1 and 2) find it difficult to maintain a voluntary contraction. The frequency of the individual units as a rule falls rapidly, and the maximal number recruited can be brought into operation for only a few moments. The number of spikes recruited in the picking-up range of the electrode in the attempt at maximal contraction in Cases 1 and 2 was at most four or five, giving rise to typical " single discharge " records (Fig. 4A). The greater part of the muscle in these cases was electrically silent. Here and there one could find individual units and, in places, also streaks with greater activity. When led off to some distance, this activity is of non-characteristic appearance, but suddenly breaks up into distinct spikes if the position of the needle is correct. Shifting of the point of the needle by a fraction of a millimetre will often suffice to bring the activity in or out of " focus."

At the next stages (Cases 3 to 5) there may still be areas which are silent or show " single discharges." In the latter case spikes of pathologically small amplitude usually occur, as well as other activity picked up from some distance ; this gives the base line a disturbed and fluffy appearance unlike " single discharges " in neurogenic disorders. The pathological process in advanced cases is apparently not uniform over the whole muscle, but often shows rather patchy distribution in regard to the extent to which the electrical activity is reduced. However, even in such severe weakness, as in Cases 4 and 5, large areas show the massed interference curve of the normal muscle. In Cases 6 to 8 the muscle everywhere showed that type of activity (Fig. 3A).

Late Distal Hereditary Myopathy.—Besides earlier ones (Kugelberg, 1947), eight additional cases (Nos. 9 to 16) of this interesting disease, which has been briefly described by Welander (1945, 1946)

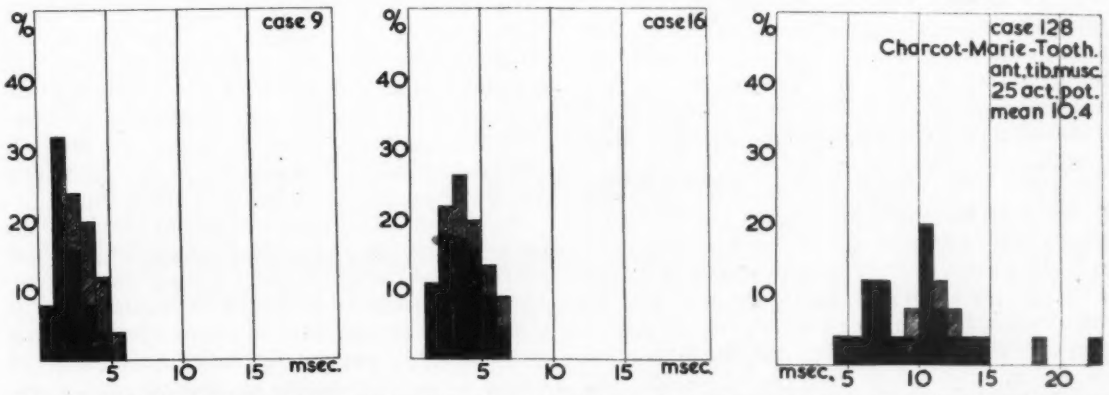

FIG. 2.—The distribution of the duration of action potentials. The portions shaded with oblique lines indicate polycylic action potentials. Cases 9 and 16, interosseous muscle in distal dystrophy, showing the shifting of the duration to the short side, in contrast to the case of Charcot-Marie-Tooth disease, with shifting of the durations to the long side.

have been examined. The cases are included in material serving as a basis for a monograph on the disease in course of publication (Welander, 1949).

As distal myopathy, "myopathia distalis tarda hereditaria," is a hitherto little-known disease, it seems desirable to give a short summary of Welander's description. Distal myopathy, as shown at autopsy, is a primary muscular disease. The heredity is dominant. The onset may occur at any age between 30 and 82, but most commonly between 40 and 50, with gradually increasing weakness and wasting of the hands, and later also of the feet. Predominantly it is the intrinsic muscles and the extensors of the distal parts of the extremities that are involved. The disease progresses very slowly and seldom affects muscles proximal to the elbow- or knee-joints, even after a duration of 30 to 40 years.

TABLE II

DISTAL DYSTROPHY
(Interosseous Muscles)

Case	Action potentials counted	Mean	Polycyclic percentage	Duration less than 3 msecs. percentage
9 (161)*	25	2·6	32	64
10 (23)	25	2·4	24	76
11 (7)	26	2·6	46	65
12 (75)	25	2·2	12	80
13 (30)	50	3·9	24	36
14 (157)	25	2·3	36	80
15 (34)	50	4·1	24	26
16 (159)	45	3·8	24	33
Normal values	20	6·5–8·8	4	approx. 4

*The case numbers in parentheses are those in Welander's monograph.

It seems scarcely necessary to enter into details regarding the electromyogram in distal myopathy, as it shows essentially the same features as the proximal forms. The average duration of the action potentials, the percentage of rapid spikes, and also the percentage of polycyclic action potentials are shown in Table II. The result, as we see, is much the same as in the proximal dystrophies. A statistically significant reduction of the average duration is observable.

In Cases 9 to 15 the interosseous muscle was severely atrophic and paretic. In Case 16 neither atrophy nor weakness of this muscle could be definitely ascertained. The patient had a strong hereditary predisposition to the disease and an undoubted weakness in the extensors of the fingers, whence it might be expected that the first interosseous muscle would also be affected. The clinical examination gave no reliable guidance in this respect. Quantitative determination, however, showed a statistically significant reduction of the average duration, as also a pathological increase in the number of polycyclic potentials and of potentials with a duration of less than 3 msecs. (Table II and Fig. 2.) Thus, though the diagnosis of "myopathy" can usually be made solely after inspection of the activity on the screen, it may be extended by quantitative determinations of the duration so as to cover even very mild cases of weakness.

Some polycyclic action potentials are shown in Fig. 5 (B–E). C–D are examples of the double spike commonly observed in dystrophy, with components of very short duration. Types C–D are hardly ever seen in the normal interosseous muscle, and very rarely in the large muscles of the extremities, but are not uncommon in the facial muscles, where the action potentials even normally have a short duration.

The interval from the beginning of the first action potential to the beginning of the second in the group is usually less than 4 msecs. In regard to the same double spike the interval is as a rule constant, though minor variations may occur. At different positions of the needle, however, the variations are considerable; sometimes the two components can be brought approximately to coincide if the position of the needle is shifted. The components may differ in amplitude, form, and duration, or they may be rather similar, as in the Figures.

Differential Diagnosis

The differential diagnosis between muscular dystrophy and lesions of the lower motor neurone in acute stages or during re-innervation is, clinically speaking, comparatively easy, and will not be discussed here. It is usually indicated by the case history. The differential diagnosis from *chronic* lesions such as degenerative diseases of the lower motor neurone may, however, be very difficult in certain clinically atypical cases. Here the electromyogram may be of decisive importance. In particular, it may be difficult in the routine clinical examination to distinguish proximal spinal muscular atrophy from the proximal forms of dystrophy, as also the Charcot-Marie-Tooth type of neural atrophy from the distal forms of myopathy.

No less than 142 cases of chronic lesions of the lower motor neurone have been investigated. Among these cases, nineteen represent the Charcot-Marie-Tooth type of progressive muscular atrophy, thirty-eight amyotrophic lateral sclerosis, four proximal spinal atrophy, fourteen anterior horn-cell lesions due to other causes, six multiple neuritis, etc. The electromyographic change, in almost every respect, differed from those in muscular dystrophy, being marked by :

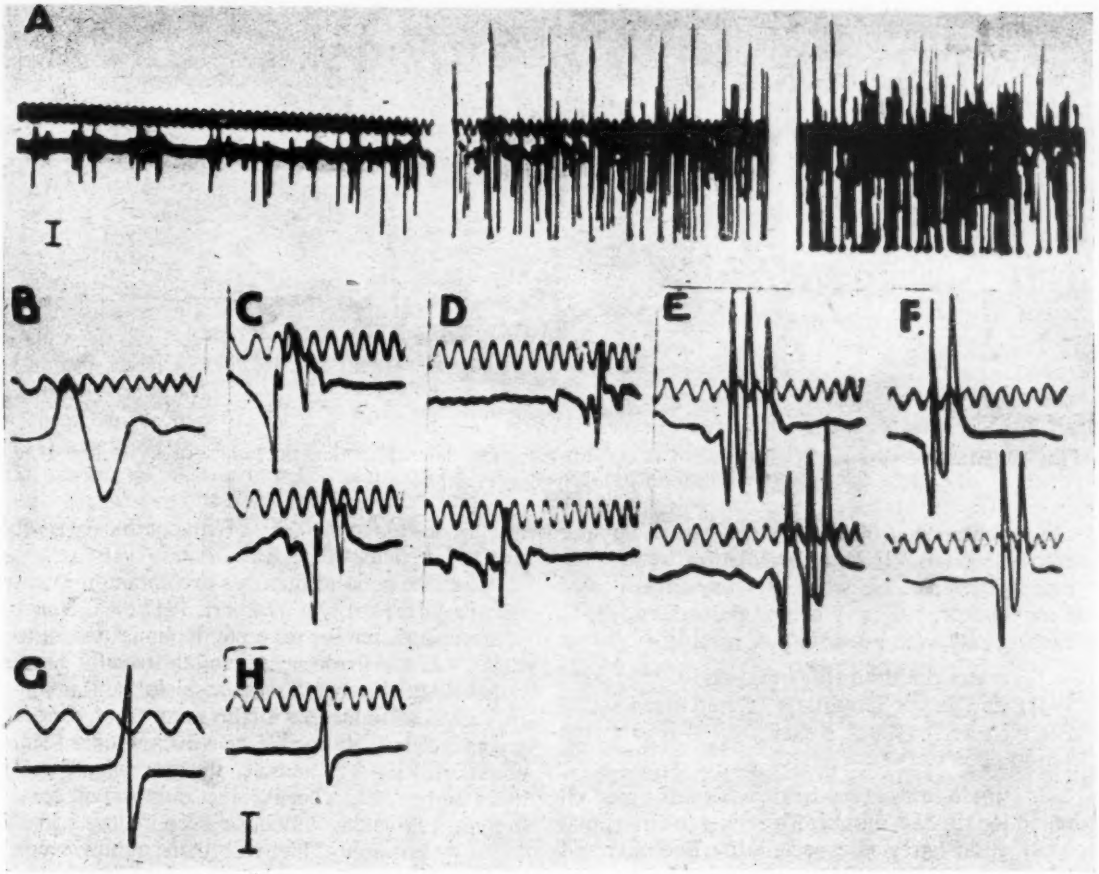

FIG. 3.—Muscular dystrophy (Case 6). Records from the biceps brachii.

A. Activity of voluntary contraction gradually increasing in strength, showing on strong contraction the interference activity of the normal muscle. Time 1/100 sec.

B. Collected action potentials with different forms and durations which are arranged B–H, to show tentatively how the normal action potential B is broken up and at last reduced to a potential H resembling the fibrillary spike. Calibration in this and the following records, 100 microvolt. Time 1/1000 sec.

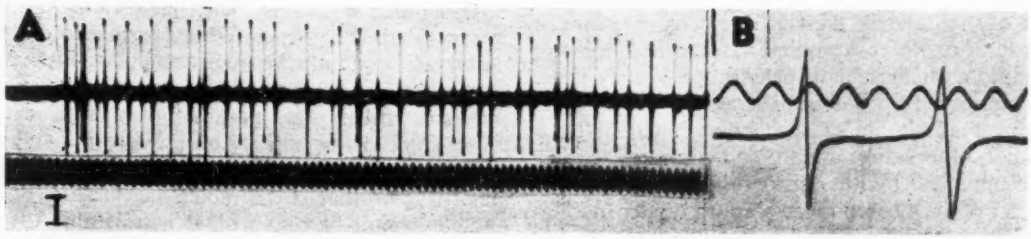

FIG. 4.—Muscular dystrophy (Case 1). Records from the clinically paralytic biceps muscle.

A. Activity at maximal voluntary contraction. Only two different action potentials are recruited. Time 1/100 sec.

B. Detail pictures of these potentials. Time 1/1000 sec.

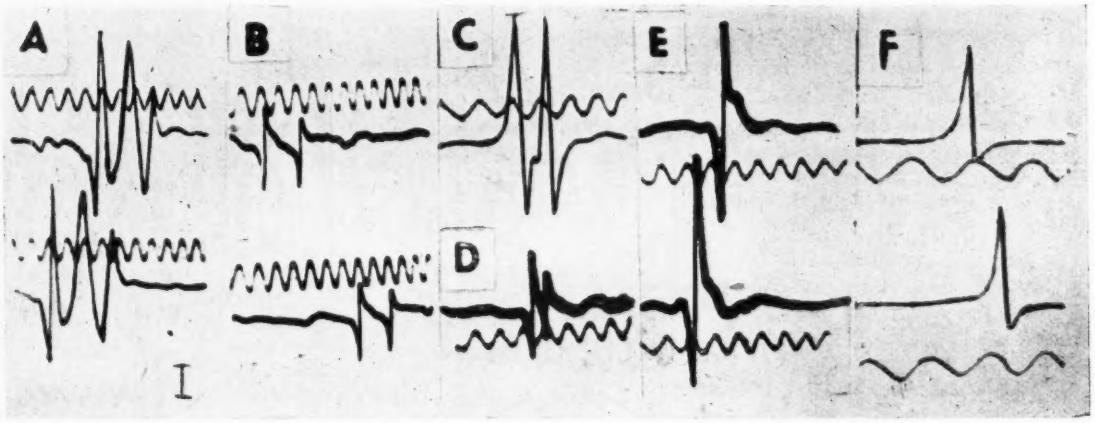

FIG. 5. Muscular dystrophy distal form (Case 10), showing different action potentials of dystrophy type. Described fully in the text. Time 1/1000 sec.

1. spontaneous fibrillations as well as greater response on mechanical stimulation by the exploring needle electrode (Denny-Brown and Pennybacker, 1938 ; Weddell and others, 1944 ; Jasper, 1947 ; and others) ;

2. greater duration (Buchthal and Clemmesen, 1941) and larger amplitude (Denny-Brown and Pennybacker, 1938 ; Kugelberg, 1947) of the action potentials.

3. even in cases of moderate weakness a marked reduction in the number of spikes on maximal contraction (stressed especially by Buchthal and Clemmesen, 1941, 1943 ; also observable with the plate electrode technique, see for example, Richter and Ford, 1928, and Altenburger, 1937).

Spontaneous fibrillation and greater mechanical irritability has always been observed in the present material during the first year after the onset in cases of extensive denervation due to acute or rapidly progressive lesions. On the other hand, such fibrillar contractions have often been lacking in cases of slight partial damage or extensive lesions of long duration where the muscle has become indurated, a symptom which is felt on penetration by the needle.

A more or less prolonged average duration as also a greater amplitude of the action potentials is a common observation in chronic neurogenic lesions, as exemplified by the histogram from Case 128 (Fig. 2) of the Charcot-Marie-Tooth type. In long-standing cases of advanced atrophy with the muscle in a bad condition, the duration and amplitude of the potentials are often normal ; or else the amplitude may even be, on an average, smaller than normal. The duration in such conditions may very rarely also be shorter than normal. This may be due to secondary changes of myopathic type due, say, to inactivity or ischæmia.

Polycyclic action potentials are common in cases of muscular atrophy (Jasper, 1947 ; as regards poliomyelitis, see for example, Rohmer and others, 1947). The polyphasic potentials usually have a rather long duration (see the histogram),

A marked reduction in the number of recruited spikes is clearly observable even in cases of moderate weakness. If, for example, the muscular force is reduced by 50 per cent., the number of spikes, roughly estimated, will have been reduced in the same proportion. One will then obtain records where the potentials cover the base-line but are definitely reduced. In certain lesions of long standing but with good functional repair we note that, despite only a slight loss of muscular force, the number of potentials is greatly reduced. Evidently the force which the average individual potentials represent has increased relatively to that which they represent in the normal muscle. The amplitude and duration in such cases are particularly marked.

By duly observing the characteristics now enumerated, it has been found possible to differentiate with certainty between muscular dystrophies and atrophies. One should, however, systematically examine the muscle, part by part, with careful observation of the activity on the screen, beginning with the muscles most affected. Should it occasionally happen that a characteristic picture of the muscle cannot be obtained, it is advisable to pass over to other muscles in different stages of disease.

Discussion

In the dystrophy cases examined, the electromyogram is characterized mainly by the following features :

1. The average duration of the action potentials is diminished, and the number of potentials with a duration of 1 to 3 msecs. is increased.

The form of the action potentials is changed in that in most cases a pathological number of polycyclic potentials is observed. They usually have a shorter duration than the average normal action potential. A diminution of the spike amplitude may be ascertainable.

2. Even if the paresis is considerable, the interference activity of the normal muscle is still found. Approximately when the muscle is just able to produce a movement in the joint, single discharges are observed.

There can be little doubt that these changes are due to a process which more or less diffusely reduces the number of muscle fibres in the different units until they are put out of action.

The action potential of the single muscle fibre, as seen in fibrillation, has a duration of 1 or 2 msecs., and an amplitude of 50 to 100 microvolts (see for example, Weddell and others, 1944). The action potential of the normal motor unit is of considerably longer duration (3 to 15 msecs.) and of larger amplitude. The generally accepted explanation of the longer duration of the latter is that not all the muscle fibres in the unit picked up by the electrode are acting in phase. The synchronization is not complete. A gradual diminution in the number of fibres composing the unit should thus, as is the case in dystrophy, tend to reduce the duration of the action potentials, and, in a minor degree, the amplitude. The reduction in the number of fibres may proceed until only a single one is left in the unit. The action potentials at this stage should be similar to those in fibrillation. In fact such potentials are by no means uncommon (Fig. 4B).

A reduction in the number of fibres composing the "motor unit" should, however, not only diminish the duration and amplitude, but also modify the form of its potential. It may, in fact, be presumed that the muscle fibres are put out of action in the unit in an irregular way—now one participating in the formation of the potential at the outset, now one acting in the middle or just at its termination. If the activity happens to be sufficiently reduced by elimination of muscle fibres except at its very outset or termination, the potential would be split up. We should then expect polyphasic action potentials. The duration of the latter, as is the case in dystrophies, should usually be shorter than that of the normal action potentials, seeing that, at all stages down to those where the unit is composed merely of a few synchronously acting fibres, they may be disintegrated in this way.

Slight polyphasity may also result from a functional disintegration of the action potential, due to disturbances in the transmission of the impulses to or through the degenerating muscle fibre. The occasional elimination of one component in a polyphasic complex indicated the existence of such disturbances. The double or triple spikes shown in Figs. 3 and 5 might also be explained by a repetitive response in the muscle fibre or end-plate. Seeing that the mechanical and electrical irritability is reduced in the dystrophic muscle, this explanation is not very convincing, but may possibly hold good in myotonia. Nor are these spikes identical with the double spikes which sometimes occur under normal conditions (Gilson and Mills, 1941; Denslow, 1948) and regularly in tetany (Turpin and others, 1943; Kugelberg, 1948a) or in ischæmia (Kugelberg, 1946, 1948b), being due to repetitivity in the motor neurone or nerve fibre (Kugelberg, 1948a and b). These spikes, unlike those observed in dystrophy, become single when the frequency rises, and the interval between them is considerably longer, about 7 msecs. The polyphasity of the action potentials is due mainly to an anatomical disintegration of the motor unit.

The marked diminution of the muscular force despite the relative maintenance of the number of action potentials indicates that the force represented by the individual potential has been reduced. This, of course, is also due to the diminution in the number of muscle fibres in the different units. The immense reduction of the average force in the units can be most clearly observed in cases of distal myopathy. Electromyographically the small hand muscles can, in fact, be far more easily surveyed and accurately controlled than the larger muscles. In order to make a minimal adduction of the second finger, only a few potentials in the first interosseous muscle need normally be brought into operation. In the diseased muscle, however, twenty, thirty, or more potentials will perhaps have to be mobilized in order to attain the same result.

The area of distribution in the dystrophic muscle of the unit represented by the action potential is moreover much smaller than in the normal muscle. If one tries to survey the area from which the dystrophic potential (1 to 2 msecs.) can be recorded, we shall find that minimal shifting of the needle will reduce the amplitude to zero. In order to get such a result in the normal muscle, the needle would have to be shifted about 1 cm. (Denslow and Hassett, 1943).

To sum up: the fact that the dystrophic process operates on the muscle fibres is the basis of the changes described in the duration, form, amplitude, distribution, and force of the action potentials.

These changes are not specific for dystrophy : they occur also in other conditions of myopathy. As has been shown, however, they give a firm basis for differential diagnosis from chronic neurogenic disorders, which do not primarily operate on single muscle fibres, but on nerve fibres, and thus on whole units.

Summary

Muscular dystrophy (eight cases of the proximal type, eight of a distal type) and various forms of chronic motor neurone disorders (142 cases) have been subjected to electromyographic analysis, with the following results.

A. The dystrophies show :

1. (*a*) The distribution curve for the duration of the action potentials is shifted towards the short side. In all recorded cases the mean of the durations showed a significant decrease, whereas the relative number of action potentials with a duration of less than 3 msecs. had increased.

(*b*) The relative number of polycyclic action potentials showed a significant increase in twelve out of fifteen cases. They usually have a shorter duration than the action potential in the normal muscle.

(*c*) A decrease of the spike amplitude may be ascertainable.

2. The interference curve of the normal muscle on maximal voluntary contraction is found also in cases of severe weakness. Roughly speaking, when the muscle is just able to perform a movement in the joint, " single discharge " is observed. The reduction in the number of spikes in advanced cases shows a patchy distribution in the muscle.

3. The strength represented by the dystrophic 1- to 3-msec. action potential, and the area from which the action potential can be recorded, are greatly reduced as compared with normal muscle.

All these changes are due to a process which, more or less diffusely, reduces the number of muscle fibres contained in the individual functional units represented by the action potentials.

B. The chronic lesions of the lower motor neurone show one or more of the following characteristics :

1. Spontaneous fibrillation. Greater response to the exploring needle electrode.

2. Greater duration and larger amplitude of the action potentials. Polycyclic potentials may occur. The latter usually have a longer duration than the average action potentials in the normal muscle.

3. The number of spikes is more or less reduced in proportion to the diminution of the muscular force. In some cases with good functional repair, however, the reduction in number is far more pronounced than the weakness. Single discharge thus occurs in moderate paresis, and in the latter case even when it is slight.

The changes in chronic lesions of the lower motor neurone are thus entirely different from those in myopathies, which is due to the fact that neurogenic disorders operate on nerve fibres and thus on whole motor units, instead of primarily on single muscle fibres and parts of units. Electromyography facilitates a reliable differential diagnosis between the two.

The Editor wishes to take this opportunity to apologise for an error which occurred when the illustrations to the article by Kugelberg published in this Journal in 1947 (see references) were being prepared for press. The electrical tracings were unfortunately allowed to be touched up by hand, and this circumstance was not discovered until after the Journal had gone to press.

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THE ANTERIOR INFERIOR CEREBELLAR ARTERY

ITS VARIATIONS, PONTINE DISTRIBUTION, AND SIGNIFICANCE IN THE SURGERY OF CEREBELLO-PONTINE ANGLE TUMOURS*

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The anterior inferior cerebellar artery arises constantly from the basilar artery on each side at the junction of its lowest and middle thirds and passes laterally and downwards to cross the cerebello-pontine angle and the eighth cranial nerve. At this point the internal auditory artery is usually given off, passing almost immediately into the internal auditory meatus. Either immediately before or immediately after crossing the eighth nerve, the main artery divides into two. (1) One branch passes laterally and downwards on the medial and anterior border of the cerebellar hemisphere. After about a centimetre or so of tortuous course it sends a constant branch of very variable size posteriorly along the medial surface of the hemisphere to anastomose with a cerebellar branch of the posterior inferior cerebellar artery. Reference will be made to this anastomosis later. (2) The other branch of the anterior inferior cerebellar artery passes directly laterally and curls round the upper edge of the flocculus, where it lies on the surface of the middle cerebellar peduncle, and it then passes on to the cerebellar hemisphere proper and anastomoses with all three main cerebellar arteries. This latter branch of the main artery which passes immediately laterally gives off small arteries which supply the middle cerebellar peduncle and adjoining part of the pons. The main artery itself also sends small vessels into the pons, supplying chiefly its lateral part as far superiorly as the junction of the upper and middle thirds and extending down to supply the lateral third of the upper part of the medulla oblongata.

Plate IIa is taken from a specimen of the basilar arterial system which has been injected post-mortem with red latex. The anterior inferior cerebellar artery on each side will be seen as described, and most significant is that part of the artery which crosses the cerebello-pontine angle, for here it lies immediately anterior to the eighth nerve and in this portion does not give off any branches. There are therefore two parts of the artery which are responsible for pontine blood supply—the main part of the vessel proximally and the lateral branch which winds round the flocculus distally. In the past few years, Dr. J. G. Greenfield has pointed out that those cases of acoustic neurofibromata which come to necropsy after operation frequently have had occlusion of the anterior inferior cerebellar artery on the tumour side by a clip or a thrombus. He also noted that this was associated with infarction of the pons on that side. In the past it has been thought that such a lesion was the result of laceration of the pons by the surgeon—in spite of his usual denial ; or it has been called *malacia pontis*.

It was therefore with this problem in mind that a series of normal hind-brains was injected with dyed gelatin solutions in various ways designed to illustrate (1) exactly which area was supplied by the anterior vessel in the pons : (2) which areas could be apportioned to the proximal and distal parts of that vessel as far as the pons itself was concerned, and (3) which anastomoses from the superior and the posterior inferior cerebellar arteries could take over the anterior inferior cerebellar arterial supply. The second question was considered the most important, because only by answering it would it be possible to ascertain the effect on life of placing a clip on the artery as it crossed the eighth nerve, that is, at the point where in effect the acoustic nerve tumour would tend to displace the vessel most away from the angle.

Variations in the Anterior Inferior Cerebellar Artery

It has repeatedly been observed that there is a considerable variation in the size and therefore in the importance of the anterior inferior cerebellar artery. Fig. 1 shows the variations and findings in a series of consecutive necropsies, and it will be seen that not only may each case be different but there is usually a difference between either

*Read to the British Society of Neurological Surgeons in Dublin in July, 1948.

This work was carried out with the aid of a grant from the National Hospital, Queen Square.

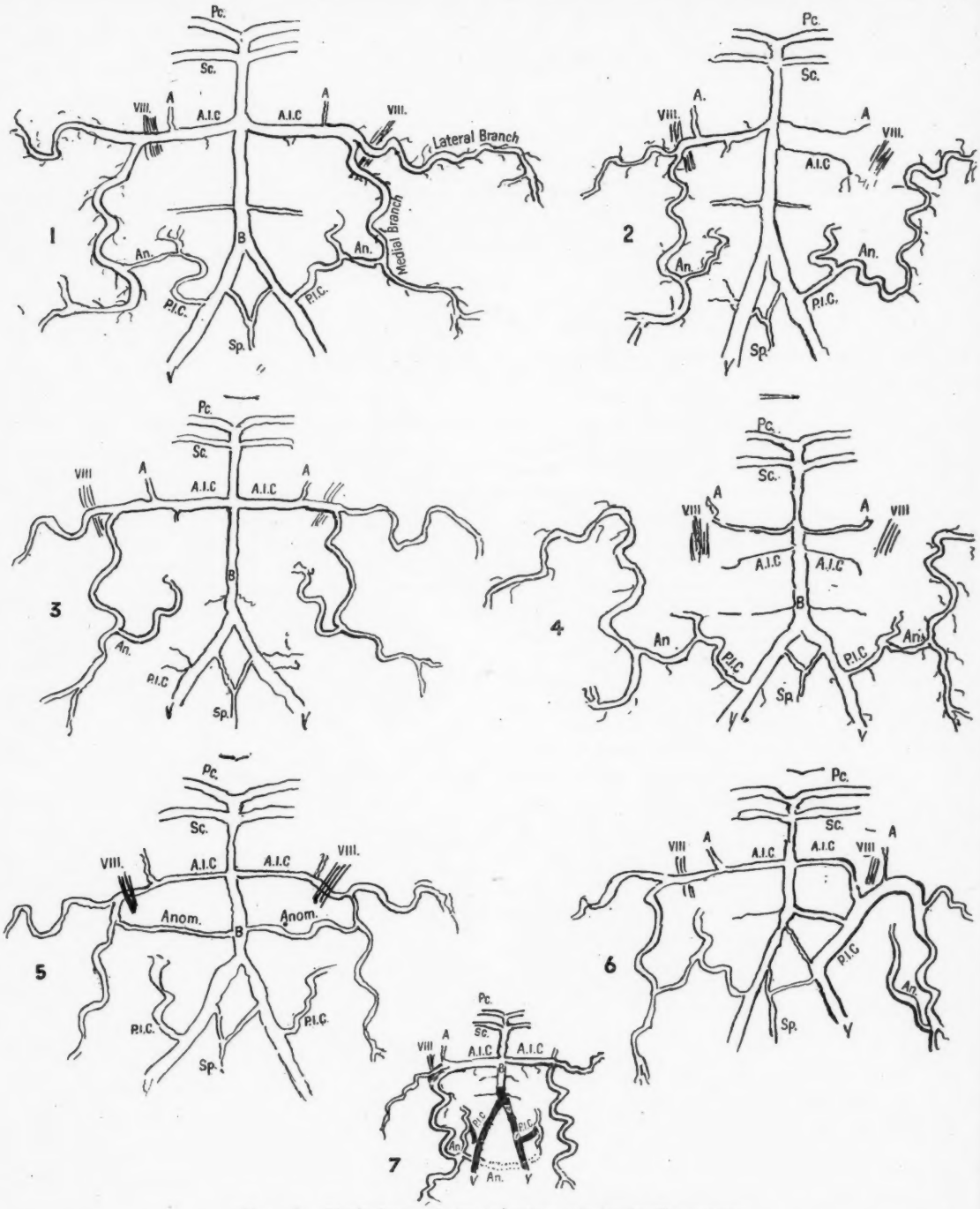

FIG. 1.—Variations of the branches of the basilar artery.

(1) The "classical" and a fairly common arrangement.

(2) The anterior varying inversely with the posterior inferior artery (common).

(3) Both posterior vessels small, their areas of supply being chiefly fed by the anterior vessels (uncommon).

(4) Both anterior vessels small, their areas of supply being chiefly from the posterior vessels (uncommon).

(5) Anomalous importance of vessel from the junction of vertebral arteries.

(6) Rare—posterior vessel being continuation of vertebral artery.

(7) Pathological—long-standing thrombosis of lower third of basilar, vertebral, and posterior arteries. Both area of supply of posterior vessels supplied by right anterior inferior artery. (Patient died from other causes.)

PC.—posterior cerebral artery; SC.—superior cerebellar artery; A.I.C.—anterior inferior cerebellar artery; P.I.C.—posterior inferior cerebellar artery; B.—basilar artery; V.—vertebral artery; Sp.—spinal artery; A.—internal auditory artery; VIII.—acoustic nerve; An.—anastomotic vessel; Anom.—anomalous vessel.

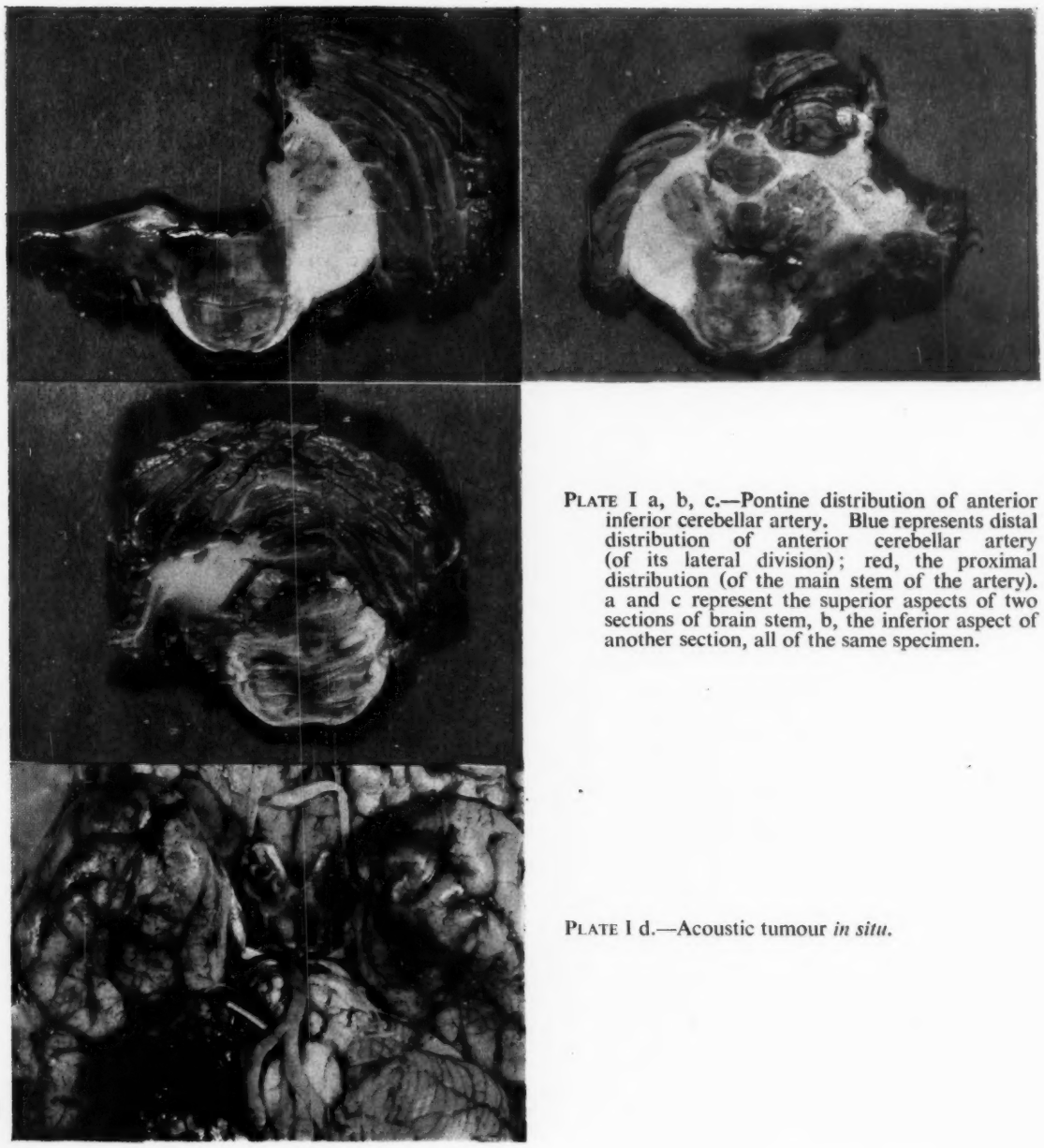

PLATE I a, b, c.—Pontine distribution of anterior inferior cerebellar artery. Blue represents distal distribution of anterior cerebellar artery (of its lateral division); red, the proximal distribution (of the main stem of the artery). a and c represent the superior aspects of two sections of brain stem, b, the inferior aspect of another section, all of the same specimen.

PLATE I d.—Acoustic tumour *in situ*.

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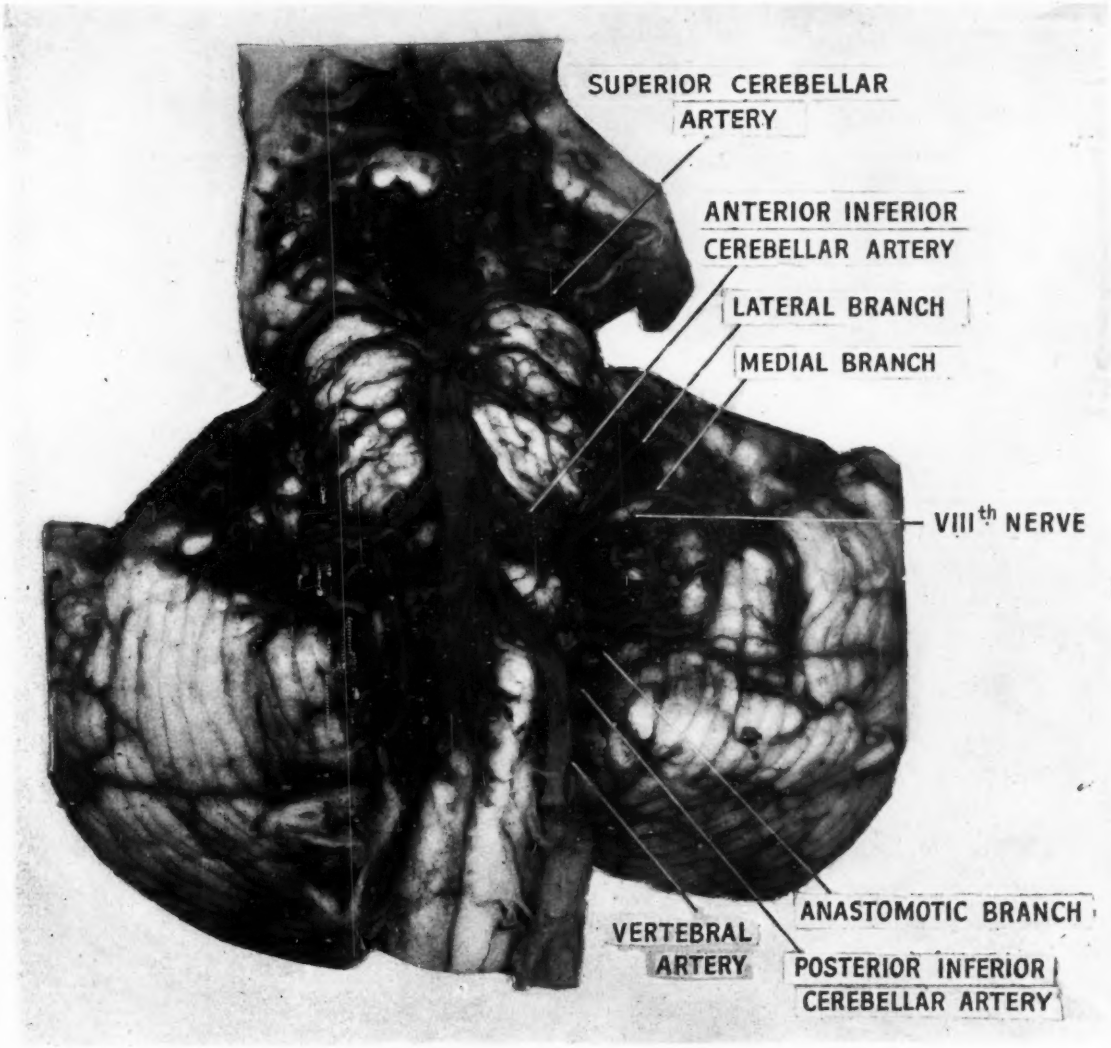


PLATE II a.—The basilar arterial system.

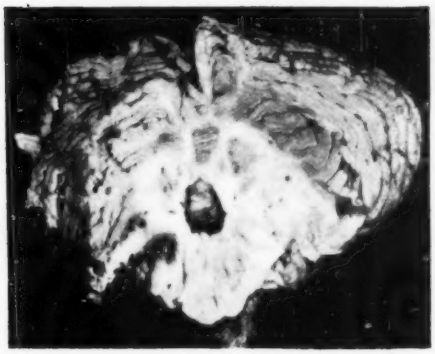


PLATE II b.—Case 1. Infarction of pons. Section through lower third of pons.

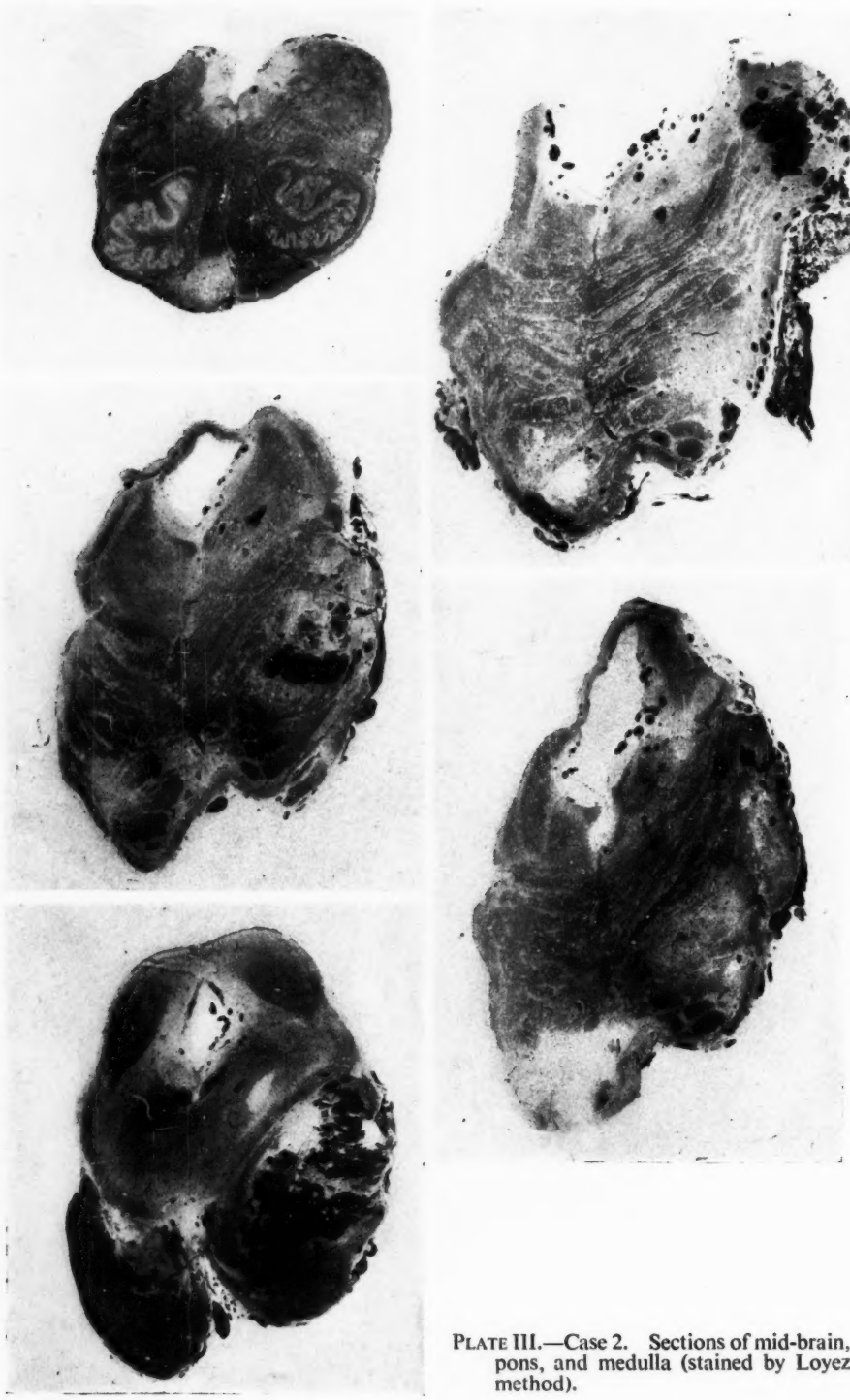


PLATE III.—Case 2. Sections of mid-brain, pons, and medulla (stained by Loyez method).

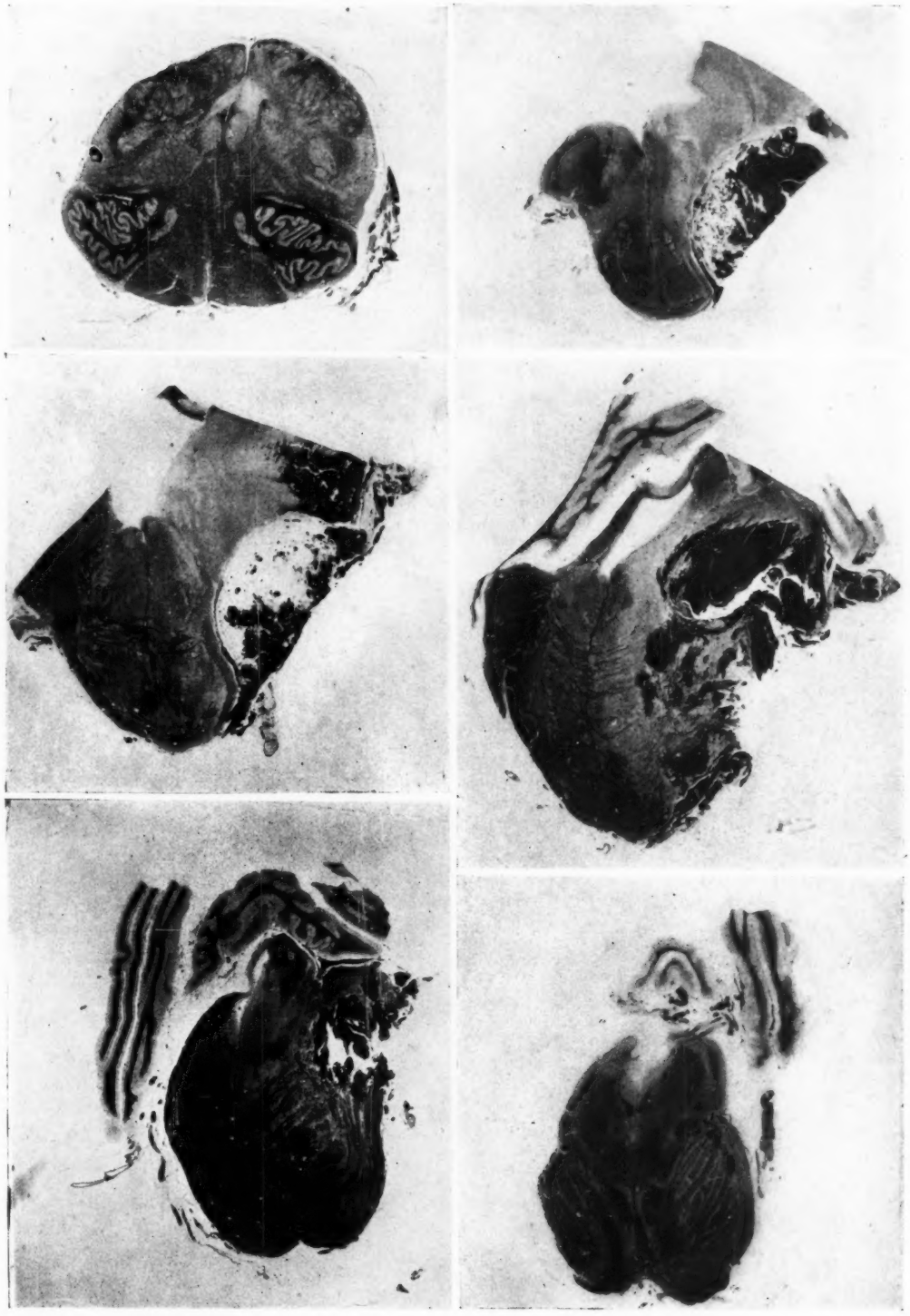
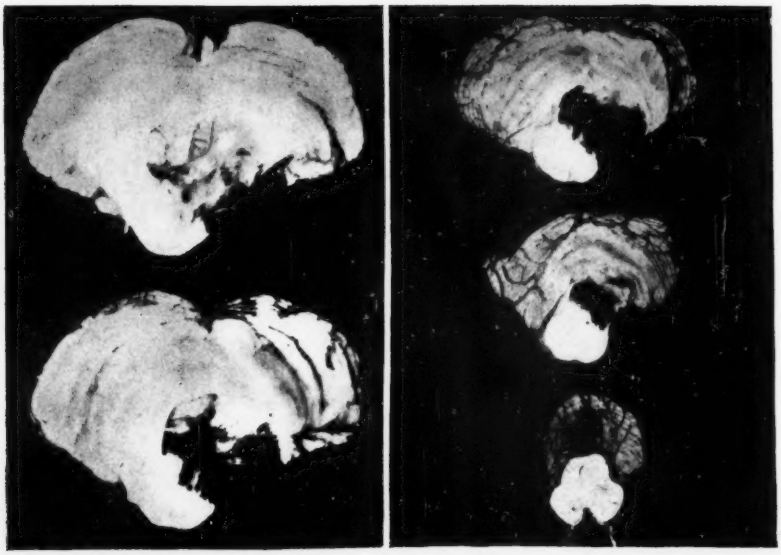
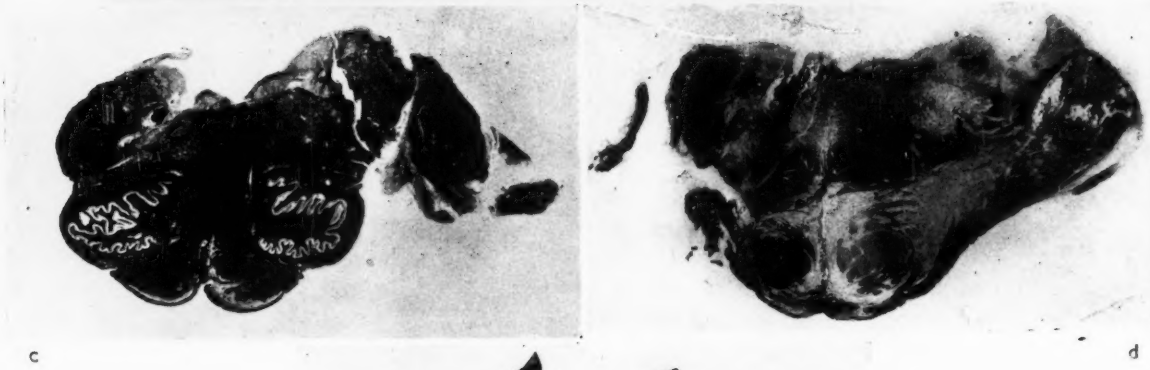


PLATE IV.—Case 3. Sections of mid-brain, pons, and medulla (stained by Loyez method).

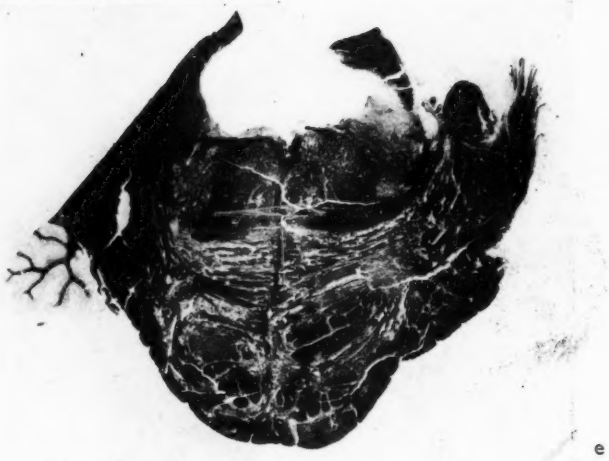


a b

PLATE V a, b.—Case 4. Sections of mid-brain and pons.



c d



e

PLATE V c, d, e.—Case 5. Sections of mid-brain, pons, and medulla (stained by Loyez method).

a

PLATE VI a.—Case 6. Section through mid third of pons (stained by Pickworth method to show vascular damage in the lateral tegmental area). Upper right corner shows fourth ventricle.

PLATE VI b, c, d, e.—Case 6. Sections of pons (stained by Loyez method).

b

c

d

e

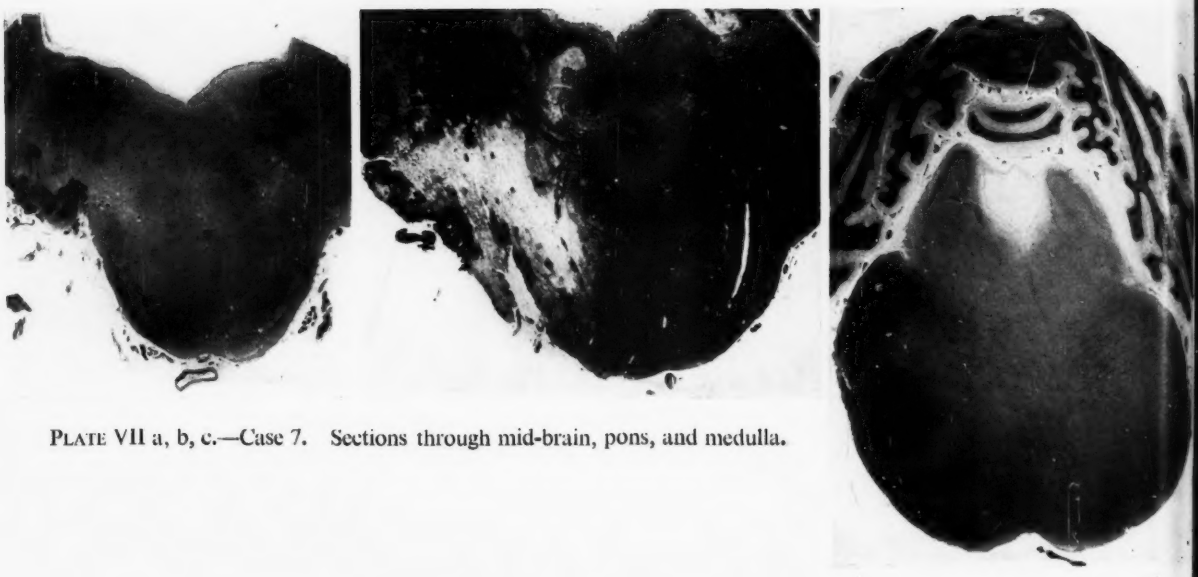


PLATE VII a, b, c.—Case 7. Sections through mid-brain, pons, and medulla.

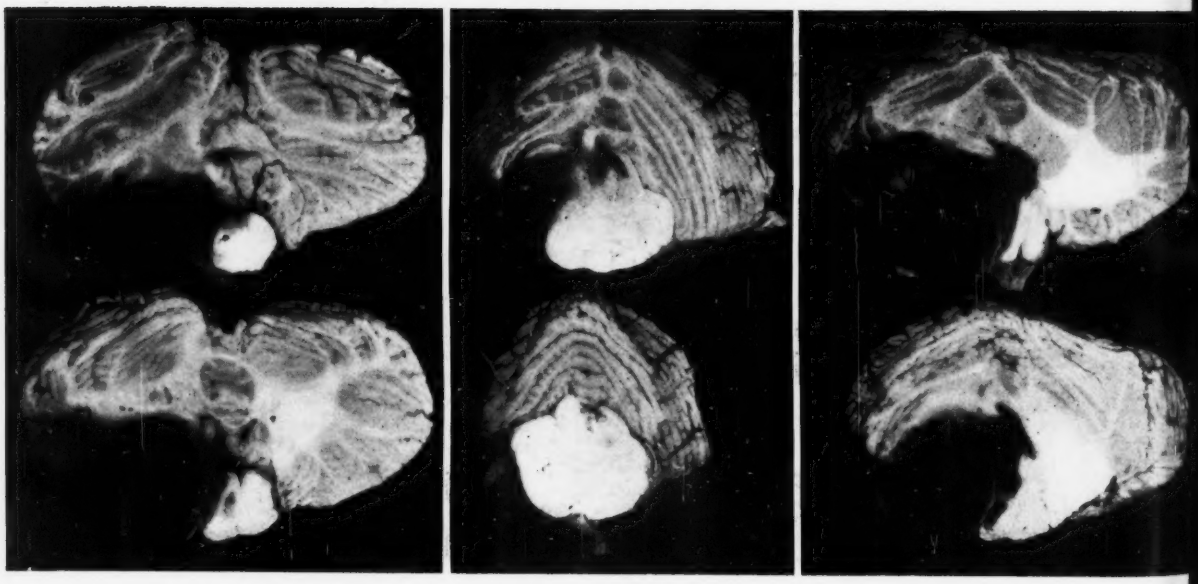


PLATE VII d, e, f.—Section of brain-stem of same case (see Plate I d) showing distribution of anterior inferior cerebellar artery after the latter's injection with blue dye.

side in the individual case. It was also found that usually this variation in size was in inverse proportion to the size of the posterior inferior artery and sometimes to that of the vertebral artery. An anastomotic vessel between the anterior inferior and the posterior inferior vessels was found constantly on the medial aspect of the cerebellum and was large where there was any marked degree of difference between these arteries on each side; its possible importance in surgery will be mentioned later. Here too was a factor that had to be eliminated in the injection of the anterior inferior artery when we attempted to outline its pontine distribution. Hæmostatic clips were placed on the cerebellar cortical anastomosing vessels, and the main proximal stem of the artery and the lateral branch were injected, after perfusing the whole basilar system with normal saline to which 1 per cent. sodium nitrate had been added. Various dyes were used to portray the areas of supply of (1) the proximal part of the artery; (2) the lateral part or branch passing round the flocculus, and (3) the remainder of the basilar system. In later investigations the areas of the posterior inferior and the superior cerebellar arteries were also injected. Plate I illustrates the area of supply of the anterior inferior cerebellar artery.

Areas of Supply

It will be seen (Plate I a, b, c) that the anterior inferior artery has two separate areas of supply —the proximal stem supplies the lateral area of the pons; and the lateral branch, after crossing the eighth nerve, supplies the middle cerebellar peduncle and an area of variable size in the lateral tegmental region of the lower two-thirds of the pons. Plate VII d, e, f represents a constant finding when the two parts of this artery are injected. We consider that the tegmentum transmits autonomic impulses which are important for cardiovascular control. This conclusion is reached from physiological evidence to be given later and from a study of other pontine pathways which can be allocated to other functions already established. A clip on the artery as it crosses the eighth cranial nerve will immediately deprive the lateral part of the tegmentum of blood supply if no anastomosis exists via the posterior inferior or the superior cerebellar arteries or the usually very small but occasionally larger (Fig. 1, No. 5) branch which may come off the basilar near its origin from the junction of the vertebrals. Further, such a clip may well initiate thrombosis in the main proximal stem of the artery and so impair the whole of the artery's pontine distribution. Moreover, we have found that, while there are numerous surface anastomoses between the cerebellar arteries over the cerebellar cortex, injection of the anterior inferior cerebellar artery from the basilar artery always stains the artery's distribution selectively. This is comparable with Bolton's (1939) work on the anterior spinal artery. She found that dye injected into a segmental spinal artery passed chiefly in a caudal direction along the anterior spinal artery, and, although a little passed rostrally by anastomosis, it did not penetrate into the capillary distribution of arteries entering at a more rostral level.

Again, it is widely held that when a main artery is injured all its tributaries and the collateral anastomoses go into spasm for a variable time. Finally, at most operations on acoustic tumours where removal is attempted, retraction of the cerebellum is invariably sufficient to produce a softening of at least part of the cortex. A certain number of anastomoses will be occluded in this manner.

Historical

Wallenburg (1901) appears to have been the first to record a lesion of the anterior inferior cerebellar artery. A clinical diagnosis of hæmorrhage from the *ramus centralis arteriæ radicularis nervi faciae dextri*, a branch of the anterior inferior cerebellar artery, was made. The patient lived seven years and at necropsy the right side of the pons appeared smaller than the left. Section revealed a hæmorrhagic cyst in the tegmentum of the pons extending to the floor of the fourth ventricle. Caudally, it reached the anterior end of the olive (inferior), and rostrally the lingula of the cerebellum. It destroyed the motor nucleus, as well as part of the sensory nucleus and some of the sensory roots of the right fifth nerve. The nuclei of the sixth and seventh nerves on the right side were destroyed, as were the nuclei of Bechterew and Deiters, parts of the restiform body and posterior longitudinal bundle, the dorsal fibres of the cochlear nucleus as they passed to the trapezoid body, and part of the spino-thalamic and spinal-tectal tracts on the same side.

Since that time there have been few observations on the place the artery may hold in physiology or medicine.

Case Records

Here it is important to consider the clinical condition of those patients who have come to necropsy and in whom there has been clear evidence of this vessel's occlusion following operation for the removal of an acoustic neurofibroma. Each case will be described in terms of operation procedure, postoperative course, and post-mortem findings.

Case 1.—The first case of which we have any record relating to the infarction of the pons was in 1938. A woman (H.W.), aged 45 years, was admitted under the care of Dr. Denny-Brown with a six weeks history of dizzy attacks and ataxia followed by vomiting attacks. On Nov. 8 she underwent the operation of partial removal of an acoustic neurofibroma ; after this she was reported as being in poor condition from loss of blood. On the next day she was conscious but had an abnormally rapid pulse rate. Two days after operation progress was reported as good although she had retention of urine. On the fourth day, however, she was comatose with a temperature of 104° F., pulse rate of 150 per minute, and normal respirations. She died on the fifth postoperative day. The post-mortem report stated that there was no excessive hæmorrhage but there was some laceration of the side of the pons in the region of the middle cerebellar peduncle on the side from which an acoustic neurofibroma had been partly removed (Plate IIb).

COMMENT.—The specimen shows what has been variously described as a laceration of the pons, presumably by the surgeon or as malacia pontis. It exactly resembles the appearance of infarction resulting from occlusion of the anterior inferior cerebellar artery, and lies in the area of supply of that artery.

Case 2.—The second case (D.C.) was in 1945 under the care of Mr. Northfield who has kindly permitted me to include this case. She had had a sub-occipital decompression in April, 1944, following a three-year history starting with weakness of the right hand. In July, 1945, a partial removal, and in October, 1945, a complete removal of the acoustic tumour was accomplished. At this operation a careful although tedious mobilization was achieved ; at the lower pole of the tumour where scar tissue attached it to the lateral cerebellar lobe a relatively small vessel suddenly bled and was clipped. The final removal was straightforward and the surface of the pons was at the end of the operation completely free from bruising. That evening the ward sister reported that breathing was deep, the head inclined back to the left, the mouth twitching and drawn to the right, the eyes turned to the left, the jaw clenched, and that there were generalized shaking movements, with the arms spastic, loss of consciousness, deep stertorous breathing, excessive saliva, pulse bounding and strong, and cyanosis. The blood pressure was 150/95 mm. Hg, the pulse 140, and respirations 28 per minute. The temperature was 102·4° F. One hour later the pulse was 120 and respirations 28 per minute and of bubbly character, the temperature being 102·4° F. She was speaking, however, and two hours after that could answer questions although she was complaining of headache. The next day lumbar puncture pressure was 250 mm. of brownish c.s.f., there being no block. Two days after operation the temperature was 104° F., pulse 168, and respiration rate 40 per minute ; she answered questions and both plantars were flexor. That evening the pulse rate rose rapidly to 176, her respiration became very bubbly, and she was cyanosed. Half an hour later the pulse rate was 200 and the respirations 32 per minute. Two hours later the pulse rate was uncountable, respirations 32 per minute, and temperature 103° F. She still continued to respond to questions. At 9 p.m. that evening, about fifty-two hours after operation, a right ventricular tap revealed a pressure of 300 mm. of crystal-clear cerebrospinal fluid. The following morning at 2.55 a.m., the pulse rate having been uncountable for the previous nine hours, the respirations became irregular and finally failed at 4.25 a.m., two and a half days after operation.

NECROPSY REPORT (Dr. J. G. Greenfield).—A silver clip was present in the anterior inferior cerebellar artery about an inch from the basilar. The right lobe of the cerebellum was destroyed except for a thin layer of the inner part of the upper hemisphere and for a bit of the lower posterior part of the hemisphere including the uvula and tonsils. The fourth ventricle was opened and ballooned towards the lateral angle. There was an extensive area of infarction involving the middle peduncle and the lateral half of the pons ; it extended inwards to a point 3 mm. to the right of the median raphe and 10 mm. to the right of the median raphe ventrally in the mid-pons plane. At the lower end of the pons this area extended into the uppermost medulla as low as a plane 3 mm. above the olive. At the lower limit of the pons the infarction reached the middle line dorsally and extended forwards 3 mm. along the mid-line and extended forwards laterally at an angle 30° from the mid-line. It did not appear to extend more than 2 or 3 mm. into the medulla. At the juncture of the pons and mid-brain there was hæmorrhage into the mid-lateral zone in the right side but not extending as high as the lower limit of the red nucleus in the territory of the right anterior inferior cerebellar artery. There was slight dilatation of the third ventricle and moderate dilatation of the lateral ventricle.

Dr. J. G. Greenfield reported that post mortem the infarcted area on the side of the pons showed on section as a partly hæmorrhagic and a partly necrotic area. In the mid-brain it involved the outer part of the crus chiefly in a hæmorrhagic manner with a zone of early necrosis between the hæmorrhage and the fillet tract. There was also a small oval area of necrosis midway between the fillet and the posterior longitudinal bundle with a small hæmorrhage near its dorsal surface, and small hæmorrhages were seen round the iter of Sylvius on the right side. At the junction of the pons and mid-brain the dorsal and external part of the crus was involved in hæmorrhagic necrosis. The fillet here was free from degeneration except for some vacuolar degeneration at its outer part but there was a zone of early necrosis dorsal to its outer end, under the wall of which small hæmorrhages were present. In the mid-pons just above the exit of the fifth cranial nerve there was much more degeneration than hæmorrhage. The degeneration involved most of the bundles of the crus except those situated most antero-medially and those lying under the emerging fifth nerve. Between this and the fillet there was a fairly large area of degeneration near the surface with hæmorrhages in a fairly wide area under the floor of the upper end of the fourth ventricle on the right side. Just below the exit

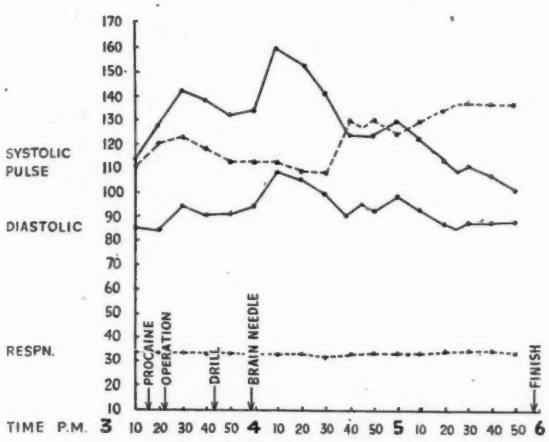


FIG. 2.—Case 3. Chart during operation of blood pressure and pulse changes.

of the fifth nerve there was a zone of degeneration extending about a third of the distance in from the surface of the median raphe with hæmorrhages into the middle cerebellar peduncle and under the floor of the fourth ventricle. No hæmorrhage or degeneration was seen in the medulla on this side (Plate III).

COMMENT.—In this case the surgeon stated definitely that following the final removal of the tumour the side of the pons was perfectly clean with no bruising or damage whatever. At necropsy, the infarct, which must have developed subsequent to operation, was in the territory supplied by the anterior inferior cerebellar artery, and the occluded artery appeared to be that which caused bleeding in the final stages of operation.

Case 3.—The third case (G.B., aged 47 years) was admitted under the care of Dr. E. A. Carmichael in February, 1946, because of deafness in her right ear for the previous three years. A piecemeal removal of a right acoustic neurofibroma was accomplished. Considerable arterial hæmorrhage was encountered in the later stages and was eventually controlled with silver clips and fibrin foam. The whole operation took three hours. One hour and ten minutes after the start the blood pressure rose from the normal 120/90 to 160/110 mm. Hg, with a fall of pulse rate from 120 to 110 per minute (Fig. 2). This slowly returned to normal over the next half hour, to remain so for a further twenty minutes. In the remaining hour it fell gradually to 110/85 mm. Hg with a pulse rate of 140. That evening the patient was very shocked, but regained a state in which she was able to respond by blinking to spoken words. Her state of consciousness did not alter from then to near the end. Blood pressure fell to 80/60 and then was unrecordable. That night a blood transfusion restored the circulatory state temporarily. She died the following morning seventeen hours after operation. At necropsy, there was a small blood clot over the bed of the tumour on the right side of the pons. "A silver clip was found on a vessel 1½" from the midline which was thrombosed back to the basilar artery and passed from the lateral surface of the pons to the infero-lateral surface of the cerebellum on the right side (anterior inferior cerebellar artery)." The right side of the pons was considerably bruised, and the middle cerebellar peduncle was very flattened by the tumour. On histological examination it was found that considerable hæmorrhagic infarction of the pons on the right side merged with an area of pallor of myelin staining which reached nearly to the mid-line at the mid-level of the pons, but nowhere involved the most ventral half of this part (Plate IV).

Case 4.—The fourth case (A.E., aged 57 years) was admitted under the care of Dr. F. M. R. Walshe in October, 1946, with pain behind his left ear and slight deafness on the left side which began four years previously. A small acoustic neurofibroma of the size of a pigeon's egg was removed. The operation note reports that an artery running over the surface of the tumour was clipped and divided. The operation took two hours, and fifty minutes after the start of operation the blood pressure rose to 150/80 mm. Hg and the pulse rate fell to 72 per minute with normal respirations for ten minutes (Fig. 3). That evening the patient failed to recover full consciousness though he reacted to stimuli. No improvement occurred with ventricular and lumbar punctures, which revealed slightly blood-stained fluid. The blood pressure remained normal but the pulse was reported as full and bounding; respirations were normal. Early the following morning, however, the

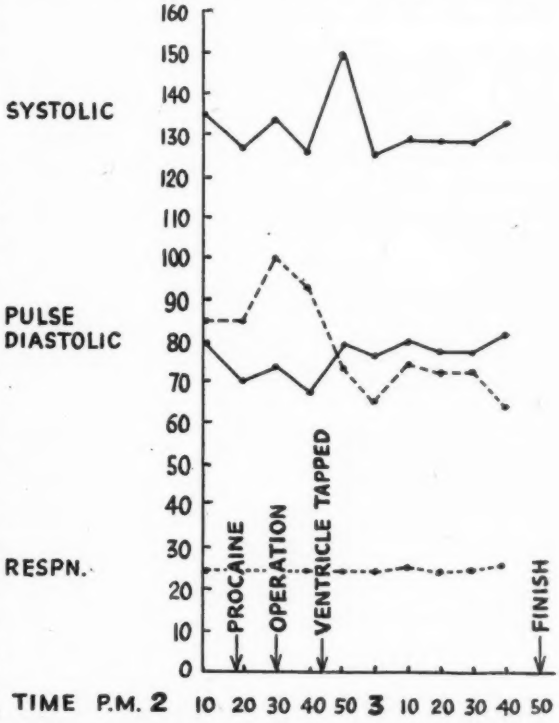


FIG. 3.—Case 4. Blood pressure, pulse, and respiration chart during operation.

condition deteriorated, the temperature rose to 102° F. the pulse was feeble—150 per minute; and the respirations stertorous, 30 per minute. He died twenty-three hours after operation.

NECROPSY REPORT.—The cavity from which the tumour had been removed was filled with half an ounce of blood clot. The anterior inferior cerebellar artery was double on this side though single on the other. The upper left artery had a free end in the region of the internal auditory meatus. Section of the pons showed almost complete destruction of the tegmentum, passing inwards as far as the mid-line against the ependymal lining and extending backwards along a line running from the central fovea of the ventricle to the outermost part of the ventral surface (Plate Va, b).

Case 5.—The fifth case (A.B., aged 58 years) was admitted under the care of Sir Charles Symonds because she had had paræsthesiæ over the left side of her face for four years.

In October, 1947, an attempt was made to remove a left acoustic neurofibroma the size of a walnut. A large artery crossing its posterior surface was double-clipped and divided, after which the capsule was coagulated and the contents evacuated with spoon and suction. The lateral portion was removed by morcellement until the uppermost nodule of growth passing through the tentorium was exposed. This was grasped with rongeurs and was delivered downwards into the wound when a sudden spurt of air followed by cerebrospinal fluid—at first clear and later blood-stained—was noticed through the indwelling lateral ventricular cannula. This spurt of fluid ceased two or three seconds after becoming blood-stained, the whole of this process lasting no more than ten seconds after the first change in the patient's condition was noticed. "Almost immediately after this first change in condition was noticed the tension of the contents of the posterior fossa became raised and the cerebellum started to herniate. The retractor had to be removed, and immediately further cerebellar herniation took place and in the space of a minute it was quite obvious that a severe hæmorrhage had taken place in the supratentorial chamber . . ." The patient's general condition had immediately deteriorated, and by the time the rapid closure of the wound had been completed the respirations were very slow and shallow, the pulse very thin and rapid, and the blood pressure unrecordable. Soon, however, her irregular respirations rose to 22 per minute with occasional deep sighs. The pulse was 120 per minute and the blood pressure rose to 100/60 mm. Hg. She remained deeply unconscious and did not respond to stimuli. The left pupil had a fair reaction to light but the right had none. The right was slightly larger than the left. She remained in this condition for a further nine hours, during which time the blood pressure slowly fell. The right lateral ventricle was tapped and clear cerebrospinal fluid under increased pressure was found. Following this, the blood pressure was said to have improved. However, her temperature rose and respirations became stertorous. She remained deeply unconscious with increasing pulmonary signs, and died twenty hours after operation.

At post-mortem examination there was no excessive bleeding anywhere and the anterior inferior cerebellar artery was found clipped and divided but not thrombosed. A small nodule of tumour one inch long and ¾ inch wide lay in the cerebello-pontine angle adherent to the brain and internal auditory meatus. There was hæmorrhagic softening of the lower pons and upper medulla on the left side. No blood clot was found in the lateral ventricles, only blood-stained fluid.

Microscopically, sections of the lower two-thirds of the pons showed swelling and punctate hæmorrhages in the lateral area including the tegmentum; this area showed as a region of pallor of myelin staining and a relative increase of interstitial spaces (Plate Vc, d, e).

Case 6.—The sixth case (B.M., aged 56 years) was admitted under the care of Dr. D. Brinton in March, 1948, because she had had attacks of vertigo for the past year. At operation an acoustic neurofibroma was completely removed from the left cerebello-pontine angle; during this procedure two arteries were exposed, clipped, and divided. At this stage, forty minutes after the first incision, the blood pressure rose sharply to 120/78 mm. Hg, having been falling slowly from 110/72 to 94/60·1, the pulse rate falling to 78. Twenty minutes later the blood pressure was 98/70 mm. Hg and at the end of the operation thirty minutes later it was 95/65. Four hours later she was conscious and rational but restless and picking at the bedclothes; five hours after operation the blood pressure rose to 150/100 mm. Hg and remained at about this level for five hours. Her temperature was 102° F. Later that day she became confused and drowsy. Three days later she was still

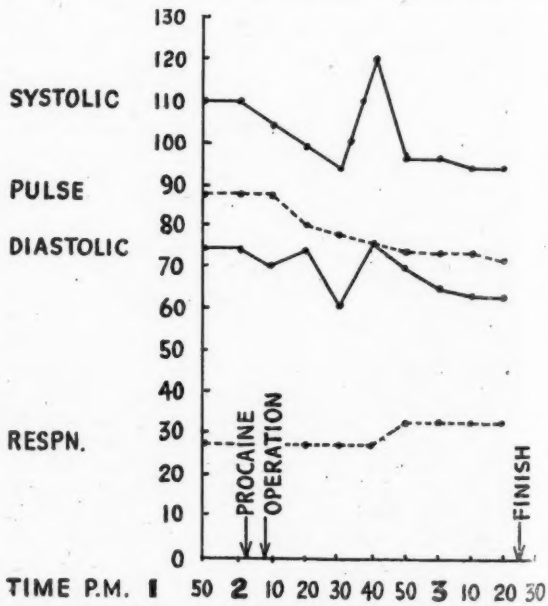


FIG. 4.—Case 6. Blood pressure, pulse, and respiration chart during operation.

stuporose; operation wound was re-opened but no hæmorrhage was found. She died on the following day (Fig. 4).

At post-mortem examination the left side of the pons in the region of the middle cerebellar peduncle was found to be swollen with a rather local protrusion, which was soft on section. A silver clip lay on the left anterior inferior cerebellar artery and a clot was attached to the vessel just short of the clip. On section of the lower two-thirds of the pons a hæmorrhagic infarct in the distribution of the anterior inferior cerebellar artery was seen (Plate VI).

Case 7.—The seventh case (J.W., aged 62 years) was admitted under the care of Sir Charles Symonds in February, 1948, because she had had attacks of vertigo and ataxia for seven months previously. A left acoustic neurofibroma was completely removed. Blood pressure

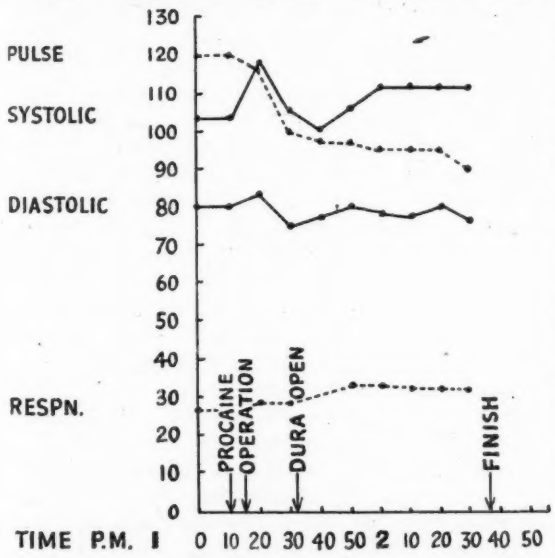


FIG. 5.—Case 7. Blood pressure, pulse, and respiration chart during operation.

remained normal throughout operation and for seven hours later. It then rose to 160/100 mm. Hg and remained at this level for at least twelve hours. On the following day her condition was fairly good although she was incontinent of urine and fæces (Fig. 5). On the second postoperative day the left cornea was observed to be ulcerated. On the third day she was drowsy and slightly confused, having increased tone in all four limbs. She also had a hoarse, irritating cough. On the sixth day she was drowsy but rousable. By evening, however, she was reported to be unconscious. The next day, seven days after operation, she died.

NECROPSY REPORT.—The right side of the pons was bruised and the right anterior inferior cerebellar artery was thrombosed where it ran outward to the internal auditory meatus. There was slight hydrocephalus. There was an area of pallor of myelin staining in the region of the junction between the lateral part of the pons and the middle cerebellar peduncle, and the lateral tegmental area was affected. Throughout this area there were microscopically punctate or ring hæmorrhages and an apparent increase of interstitial spaces (Plate VIIa, b, c).

COMMENT.—This is the only case without operative occlusion of the vessel; thrombosis obviously took place later. This time the operation chart did not reveal any autonomic change although in the subsequent twenty-four hours the pulse pressure did alter in a manner similar to that seen in the other cases.

Discussion of Cases

The above series of seven cases consists of one from Chase Farm Hospital and six from the records of the National Hospital, London. These six occurred between 1938 and 1948 and all died following the complete or nearly complete removal of acoustic nerve tumours. During the same period there were eight other deaths from acoustic nerve tumours at the National Hospital. In one case no operation was performed, two underwent suboccipital decompression only, and five had both partial removals and suboccipital decompression. None of these cases had pontine infarction as described above.

The operation and postoperative records are given in the cases described because it appears that clipping or injuring the artery may be associated with autonomic disturbances. The blood pressure rose at or near the time when the artery was occluded, but soon subsided and in most cases the immediate postoperative state seemed fairly satisfactory. However, the pressures in the lumbar theca and lateral ventricles, when taken, remained high; consciousness was disturbed and there were many signs of generalized increase of intracranial pressure. The final deterioration resembled very closely that seen in patients dying of supratentorial tumours.

Correlation of Data

It will be seen that the area of infarction of the pons in these seven cases coincides almost exactly with that area which accepts the dye when it is injected into the anterior inferior cerebellar artery. The area we consider to be of primary importance, as far as the patient's life is concerned, is the tegmental area. This point will be elaborated later.

The lateral branch of the artery which winds around the flocculus sends back branches to this area which would therefore be involved if the clip were placed on the artery as it crossed the eighth nerve. Further, the possibility of retrograde thrombosis provides an explanation for an ischæmia of the tegmental area, even if the latter were supplied

by the main stem of the anterior cerebellar artery. There appears to be little or no intrapontine anastomoses between arteries penetrating the pons or the middle cerebellar peduncle. The anastomotic supply via the posterior inferior cerebellar artery may be lost if this artery is relatively small on one side. The previously stated findings that anastomoses do not permit ready overflow from one arterial distribution to another and that spasm tends to occur in the branches of the injured artery, are also factors which may impair the recovery of circulation after occlusion of the vessel.

The study of autonomic disturbances from brain-stem injury has interested many physiologists and clinicians, and it is the effects of such injury which still prevents success in the treatment of conditions raising intracranial pressure.

It is interesting here to note that Le Beau and Bonvallet (1938) obtained a state of cerebral swelling in the supratentorial cerebral tissues, associated with a rise in blood pressure, following sections of the brain stem from the medulla oblongata up to the thalamus. They submit that the rate at which "cerebral œdema" took place was related to the rise in blood pressure. A recent publication by Le Beau (1948) deals with this subject further. Kabat and others (1935) have shown that lesions in the region of the central tegmental tract, whether in upper pons or mid-brain, give rise to alterations in blood pressure in animals. A lateral tegmental lesion in the middle third of the pons in the cat also produces a similar rise of blood pressure (personal observation); this area coincides with that of the blood supply from the anterior inferior cerebellar artery. A further contribution on this subject is being prepared.

There are many implications arising from this work, and it is suggested that the rise in blood pressure which takes place during the course of the operation on an acoustic tumour at about the time when the anterior inferior cerebellar artery is occluded is caused by an ischæmia of the lateral tegmental area in the region of the pons supplied by that artery. What precisely happens to the cerebral and pulmonary circulations when the lateral tegmental areas are injured is at present a matter for further detailed investigation. The autonomic pathways in mid-brain and pons convey impulses for vasomotor and respiratory regulation, disturbance of which somehow sets up an irreversible process whereby the brain swells and the lungs become œdematous.

Some findings which surgeons have reported are relevant here. First, as the surgeon approaches the pons, usually during the latter part of the removal of the tumour, the blood pressure is often noted as rising temporarily to 160/100 mm. Hg with a fall in pulse rate. This is sometimes ascribed to the removal of that last part of the tumour in the tentorial hiatus. I submit that it may be due to a spasm of the anterior inferior or superior cerebellar arteries impairing the blood supply to the lateral tegmental areas. This vasomotor change does not usually persist, and Beattie and others (1938) showed experimentally that after permanent unilateral lesions in the pons, mid-brain, or lateral hypothalamic area, the blood pressure tends to come down again to normal after an interval.

Secondly, the cerebellum is seen to bulge suddenly down into the wound and the intraventricular pressure to rise acutely as shown by the indwelling cannula in the lateral ventricle. Such an event is often attributed to the anæsthetic; but another explanation may well be that the blood pressure, and the supra-tentorial pressure, rises as the lateral tegmental area is deprived of blood supply by the occlusion of the anterior cerebellar artery. Thus acute cerebral compression results, and the vicious circle of supra-tentorial compression occurs.

Thirdly, in two other cases following this type of operation complete anæsthesia of the ipsilateral side of the face and dissociated sensory loss of the opposite side of the body have been observed. This is probably due to infarction affecting the lateral pontine area in the region of the entering fifth nerve and its principal sensory nuclei and the spino-thalamic tract.

In conclusion, the chief implication of this work is that there is a grave danger to the patient if the anterior inferior cerebellar artery is occluded during the operation on an acoustic tumour. This danger is in damage to the autonomic pathways from infarction of the tegmentum of the pons. It must be conceded that there are many cases of recovery in which the anterior inferior cerebellar artery has been intentionally occluded at operation. However, if at operation the posterior inferior cerebellar artery were found to be unusually small it would be reasonable to infer that the anterior inferior cerebellar artery is large and that there is likely to be only a poor collateral circulation via the posterior vessel: in which case its operative occlusion might be dangerous.

Summary

1. The course, distribution, and anastomotic relations of the anterior inferior cerebellar artery are described.

2. Seven cases of acoustic neuroma are described in which an infarction of the lateral tegmental region of the pons, in the area corresponding to

the distribution of this artery, was found at necropsy, soon after operation. In all these cases there was occlusion of the vessel in the neighbourhood of the internal auditory meatus, either due to a clip placed on the vessel at operation or to post-operative thrombosis of the artery.

3. These cases suggest that occlusion of the anterior inferior cerebellar artery is an important cause of death after operation, especially when this artery is larger than usual. The recognition of an unusually small posterior inferior cerebellar artery may warn the surgeon that the anterior inferior artery is dangerously large.

4. An attempt is made to correlate certain clinical observations made on these cases, especially the rise of blood pressure following interference with the anterior inferior cerebellar artery, with the results of experimental lesions in the lateral tegmental region of the pons.

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SOME UNUSUAL COMPLICATIONS OF HERPES ZOSTER

BY

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Herpes zoster is a virus infection which attacks primarily the posterior nerve root ganglion and adjacent spinal grey matter. Head and Campbell (1900), though unaware of the causative agent, termed it an acute posterior poliomyelitis. However, more extensive involvement of brain and spinal cord, including motor neurones, may occur. It is an infection which usually gives prolonged immunity. Van Rooyen and Rhodes (1940) considered that recurrent zoster was extremely rare. When it does occur, attacks are usually separated by years. The three cases described below illustrate unusual clinical manifestations of the condition. All three had clinical evidence of myelitis situated at the central end of the nerves involved in the zoster. In two the infection pursued a migratory course, passing through several segmental skin zones with a few weeks' interval between the involvement of each. The third case illustrates the precipitation of a zoster infection by trauma to a nerve. Such " symptomatic " zosters are recognized, but in these cases the sequel of an encephalitis or myelitis, which occurred here, is not usual.

Case Histories

Case 1.—A widow, aged 73 years, in July, 1947, developed an unpleasant tingling feeling in the skin of the left buttock. Within forty-eight hours a typical herpetic rash appeared, which spread to involve the right buttock, so that she had a saddle-area herpes zoster of the third and fourth sacral segments. Four days later she developed urinary retention with overflow, for which she was admitted to hospital. This required catheterization for five days. Thereafter voluntary evacuation was possible, at first with the aid of manual pressure. When she left hospital sixteen days after the onset of the retention she was passing urine normally except for a slight stress incontinence that had been present previously. She remained well for about two weeks. Then, some five weeks after the first zoster eruption had appeared, there was a second outbreak, after the usual prodromal skin sensation, this time below the shoulder blades in the sixth dorsal and parts of the seventh dorsal areas. This outbreak was also bilateral. The rash cleared, leaving some residual burning pain in the area. One month later the left trigeminal nerve was affected, mainly in the second division, and in a few days this spread to involve the second and then the first division of the nerve on the right side. Thereafter she remained well until August, 1948, when she developed an isolated left facial palsy of peripheral type. No vesicles were found, and there was nothing to suggest that this was linked with her previous zoster. The cerebrospinal fluid was not examined. No contact with chicken-pox was recalled.

Case 2.—A married woman, aged 58 years, had had an attack of herpes of the left buttock in 1937. In June, 1948, she developed a zoster infection of the left trigeminal nerve. Vesicles were mostly in the second and third division areas. She also complained of diplopia, especially with lateral eye movements. About ten days later vesicles appeared on the right side of the neck in the second to fourth cervical segments. The condition cleared and she was well for about two weeks. At this time a few scattered vesicles formed on the left side of the neck in the third and fourth cervical segments. These subsided rapidly. Three to four weeks later she developed severe itching in the area of all three divisions of the right trigeminal nerve. A few vesicles formed in the first division area. During the following week she noted some drooping of the left and then of the right eyelid, and diplopia in all directions for distant objects. Examination at this time showed bilateral ptosis, left more than right, some lateral nystagmus, with a tendency to skew deviation, and uncrossed diplopia present in all directions. There was marked hyperæsthesia throughout the territory of the right trigeminal nerve. The pupils were 3 mm. in diameter, equal, central, and circular, and reacted to light and accommodation. No asymmetry of sweating or temperature could be felt in the face. There was no evidence of long tract involvement. The cerebrospinal fluid contained three lymphocytes per c.mm. and 40 mg. of protein per 100 c.cm.

A few days later she showed increased ptosis, complete on the left side, and developed an unsteady gait and difficulty in starting micturition. Examination revealed an extensor plantar response on the right side, and an absent plantar response on the left. These features persisted for a week, after which the ptosis cleared up, followed by the bladder symptoms and ataxia. In a fortnight's time the only remaining abnormalities were diplopia on looking to the left and the plantar responses as above. Three months after the onset of the second phase of her illness the patient was up and about normally, but still complained of slight diplopia.

Case 3.—A farm labourer, aged 43 years, was seen in January, 1948, suffering from severe trigeminal neuralgia of the second division on the right side, of six weeks' duration. There was a history of a previous attack eight months before, when extraction of carious teeth had been followed by cessation of pain. At the time of this first attack he had complained of unsteadiness of the right leg, though examination then showed no abnormality of the central nervous system. During the second attack also there was an indefinite history of ataxia on one occasion when the patient was walking in the dark, but again the nervous system was normal. In view of the limited zone of pain, an alcohol injection of the infraorbital nerve was done. This produced anæsthesia of the appropriate area and some reduction in the intensity of the pain. Three days later the patient developed a zoster eruption of the whole skin area of the second division of the right fifth nerve. Within a week of this incident signs of mid-brain involvement appeared and progressed rapidly. Examined at this time he had nystagmus, vertical as well as lateral, skew deviation with diplopia, slight dysarthria, and incoordination with intention tremor of right arm and leg movements. The cerebrospinal fluid showed 40 mg. of protein per 100 c.cm. and no cells. The signs subsided slowly over a period of six weeks. There was no history of exposure to chicken-pox.

Discussion

Three points are of interest in these cases. First, all three showed signs of myelitis accompanying the cutaneous zoster. This complication, known since the end of the last century, has been well recognized since the full discussion of it under the title "myelite zosterienne" by Lhermitte and Nicolas (1924). Some degree of localized posterior myelitis is probably frequent in these cases. It is shown clinically only if it extends to involve long tracts, or passes forwards to anterior horn cells. The histological picture, discussed by Head and Campbell (1900) has recently been elegantly demonstrated by Denny-Brown and others (1944).

Secondly, Cases 1 and 2 raise a problem in the development of immunity to the zoster virus. There is much clinical evidence—chicken-pox follows contact with herpes zoster, though the reverse is less common—which supports the immunological studies of Netter and Urbain (1926) on the identity of this organism with that causing chicken-pox. Immunity produced by an attack of either of these conditions is usually prolonged. Second attacks are rare, and if they occur they do so many years after the first (Hruszeck, 1934; Graham-Little, 1937). During an attack of zoster, vesicles may spread to other dermatomes than those first involved, or a generalized eruption may follow. In either case, this usually occurs during the first five days after the first eruption (Weber, 1916; Brain, 1931), though cases are mentioned where new blebs appear up to ten or eleven days later, and in one a fresh eruption in the originally affected zone seven weeks later (Schiff and Brain, 1930; Denny-Brown and others, 1944), while Bokay (quoted by Brain, 1931) recorded a generalized eruption following as long as three weeks after a local zoster. Presumably after this interval, which in most cases is of a few days' duration, the ultimately long-lasting immunity has been established. The mode of production of such immunity in certain virus diseases is in doubt. One view is that after the initial infection the virus maintains itself within the cells of the host. Its rate of reproduction is adjusted so that enough is formed to infect the host cell and any daughter cells derived from it, but not enough to cause clinical manifestations of the disease. A state of true symbiosis is thus achieved. In some diseases, notably herpes simplex, the balance between virus growth and cell function can be easily upset by some general infection or even local trauma, with the production of clinical herpes simplex. In other conditions, of which herpes zoster and chicken-pox are examples, the virus/host cell symbiosis is assumed to be more stable. Second attacks of these diseases are supposed to occur by reinfection after the virus from the first attack has died out.

However, in the two cases discussed here such a sequence of events did not seem to occur. No effective immunity was established by the attacks, at any rate for two or three months. This clinical course is more reminiscent of a herpes simplex than of a zoster infection, and this possibility must be considered. The presence of central nervous system involvement does not exclude such an interpretation, as this complication with herpes simplex has been recorded sporadically during the last 45 years (Howard, 1905; Whitman and others, 1946), severe and even fatal encephalitis being noted (Swan, 1943). If this be the explanation, then it must be recognized that a vesicular eruption of dermatome distribution and with other clinical characters of a zoster may in fact be a herpes simplex. Alternatively, something may have prevented or delayed the development of normal immunity to the zoster virus, in which case it must be borne in mind that immunological behaviour of the type shown in these cases is not incompatible with infection by this virus. The solution to the problem would be given by identification of the causal agent. Antigen/antibody studies in such cases are complicated by the fact that 50 per cent. of the population, usually with a history of recurrent herpes simplex, have circulating antibodies to this virus (Andrewes and Carmichael, 1930), so that their presence in a given case is no proof that a herpetic eruption is necessarily due to the simplex

virus. Direct isolation of the virus from the cerebrospinal fluid or vesicles would probably be necessary to provide an unequivocal answer.

Thirdly, Case 3 exemplifies a "symptomatic" zoster, secondary to peripheral trauma of the fifth cranial nerve. This is not uncommon after involvement of the first sensory neurone, especially at root level, by secondary neoplasm or tuberculous granuloma. Its cause is generally supposed to be the zoster virus, trauma being only a precipitating factor (Brain, 1931). Such a view is supported in this case by the sequel of mid-brain encephalitis, inexplicable on a purely traumatic ætiology. A further question arises here. Could the mid-brain signs represent an exacerbation of a pre-existing mid-brain lesion of which the original tic douloureux was itself a symptom? Such a lesion might be a latent virus encephalitis whose symbiotic balance was upset by trauma to the fifth nerve, or it might be a separate lesion aggravated by infection of the fifth nerve ganglion and its central connexions. In our case the known absence of pre-existing mid-brain signs supports the simpler explanation that the encephalitis depended on the preceding zoster infection. The question arises to some extent in any case of this condition with central nervous system complications, especially if they are distant from the segmental area first involved. This has been discussed at some length by Schiff and Brain (1930). Pre-existing infection has to be considered also when zoster follows root section in the treatment of an apparently "idiopathic" trigeminal neuralgia, a not very uncommon sequence. The answer must await further knowledge of the behaviour of neurotropic viruses.

Summary

Three cases of herpes zoster are described. All showed myelitis as a complication of the infection. Two had recurrent attacks of zoster in different skin zones over a period of two or three months, thus showing a marked difference from the usual behaviour of the zoster virus, which confers life-long immunity by a single attack. The possibility that these were really cases of herpes simplex is mentioned. The third case had a zoster infection precipitated by injury to the fifth nerve. The relation of virus infection to such precipitating factors is briefly discussed.

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PINEALOMA WITH A SOLITARY SPINAL METASTASIS

BY

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In forty-two cases of tumours of the glioma group giving rise to metastases, Polmeteer and Kernohan (1947) found only one pinealoma. In this case, which is recorded in detail by Bagenstoss and Love (1939), the tumour filled the third ventricle and had become implanted in the other ventricles and on the roots of most of the cranial nerves. The spinal cord was not examined. These authors also describe a second case in which a tumour having the cytological structure of a pinealoma was found at operation behind the optic chiasma. Fourteen months later laminectomy at the level of the twelfth dorsal vertebra revealed intra- and extramedullary tumours, two of which were examined histologically and showed a structure similar to that of the original tumour. It was not stated whether the presence of a tumour in the region of the pineal gland was ever proved in this case. There are several other instances in which pinealomas have given rise to metastases in the ventricles or around the base of the brain. Horrax and Bailey (1925) described three cases but in only one was the structure that of an adult type of pinealoma, and this showed implants limited to the third ventricle. Fulton and Bailey (1929) record another in which there were deposits in the ventricles and partial destruction of the pituitary gland and infundibulum by tumour infiltration. Berblinger (quoted by Bagenstoss and Love), reported a case of a pinealoma with metastases in the spinal cord and cauda equina.

Friedman and Plaut (1935) describe a case in which there was diffuse infiltration throughout the meninges, cranial and spinal nerves, and ganglia by large and medium sized cells without stroma, and at the site of the pineal gland there was a nodule the size of a pea which was found histologically to consist of the same type of cell as that in the other tumour masses. Neither in the so-called primary tumour nor in the metastases was the usual mixture of two types of cell seen, and it appears to us that the origin in the pineal gland, although suggestive, is not definitely proven. Ford and Muncie (1938) saw three cases of diffuse tumour infiltration of the ependyma of the third ventricle which histologically somewhat resembled a pinealoma with large and small cells, but in each case the pineal gland was normal. Stringer (1933) described a solitary implant in the tuber cinereum but the spinal cord was not examined.

We can find no record of a previous case of pinealoma in which there was a large solitary spinal metastasis, and we believe our case also to be unique in that the deposit formed a dumb-bell tumour.

Case Report

A healthy-looking dockyard worker aged 31, was admitted on May 30, 1948, to the Surgical Unit of the Cardiff Royal Infirmary, under the care of Professor Lambert Rogers. The patient had been well until three years previously, when he began to have attacks of aching pain over the tip of the left shoulder. These attacks, lasting for hours or days, were followed by periods of remission of several weeks or months. During the latter part of March, 1948, the pain in the left shoulder became more severe, radiating to the lower cervical region, across to the tip of the right shoulder, and down the outer side of the left arm. About six weeks later he noticed that he could not move his left arm as well as usual, and within a few days the arm became paralysed, so that on May 20 he was admitted to another hospital suspected of suffering from anterior poliomyelitis. Four days later he had developed weakness of his left leg, and he was transferred to the Cardiff Royal Infirmary with the provisional diagnosis of spinal-cord tumour.

On examination a firm elliptical mass could be palpated at the base of the left anterior triangle of the neck. The long diameter of the tumour lay in the direction of the brachial plexus, and the mass was slightly movable from side to side but not up and down.

The muscles of the left arm and hand were wasted, the tendon reflexes were diminished, and voluntary movements were greatly reduced. There was loss of power in the biceps, in the flexors and extensors of the wrist and fingers, in the triceps, and in the small muscles of the hand. There was bilateral loss of pain sensibility below the level of the wrists and of temperature sensibility below both elbows.

Below the level of the cutaneous distribution of the second dorsal nerve there was a right-sided hemianæsthesia for pain and temperature but no loss of deep or tactile sensation. The left leg showed spastic paresis and an extensor plantar response, that of the right foot

being equivocal. The cranial nerves were intact and there was no papilloedema.

By lumbar puncture the cerebrospinal fluid was found to be at a pressure less than atmospheric. The Queckenstedt response was sluggish, and there was a marked plateau on release of jugular compression. The fluid was clear and colourless and contained 30 lymphocytes per c.mm. and 75 mg. of protein per 100 c.cm. The Lange colloidal gold test was normal and the Wassermann reaction negative. An *x*-ray examination of the cervical spine showed slight enlargement of the fourth intervertebral foramen.

During the first week in hospital a flaccid paresis of the right arm developed, and on the tenth day the patient suddenly became cyanosed and had great difficulty in breathing, the temperature rising to 102° F. and the pulse rate to 120 per minute. The intercostal muscles were found to be paralysed and he was placed in a mechanical respirator.

Operation (Performed by H.R.I.W.).—With the patient in the iron lung, anæsthesia was induced with cyclopropane, and the patient transferred to the operating table, where controlled anæsthesia was maintained and cervical laminectomy performed. A tumour was felt within the dural envelope at the level of the fourth and fifth cervical vertebræ, and there was a small soft extradural extension at the level of the fourth cervical nerve root. When the dura was opened an elliptical soft maroon-coloured tumour, approximately 4 cm. long and 1 cm. thick, was exposed. This tumour, which was very hæmorrhagic, was adherent to the dura and to the lateral aspect of the spinal cord, the latter being compressed and displaced towards the right. The spinal roots disappeared into the tumour substance. A small piece was removed for biopsy, a wide decompression performed, the dural tube sealed with "Gelfoam," and the wound closed in layers.

The patient's condition remained critical throughout the operation and no improvement followed decompression. He died shortly after being transferred from the operating table back to the iron lung.

Necropsy Findings.—The brain showed no evidence of increased intracranial pressure. There were no medullary or tentorial pressure cones. The pineal gland could not be identified but was replaced by a soft, well circumscribed greyish-pink tumour which was about 3 cm. in diameter and which did not invade any surrounding structures (Fig. 1). There were a few petechial hæmorrhages on the floor of the fourth ventricle.

In the spinal canal there was a little blood in the subarachnoid space, and at the level of the bodies of the third, fourth, and fifth cervical vertebræ there was a fusiform greyish-pink tumour lying mainly subdural and partly extradural, lateral to the spinal cord on the left side (Fig. 2). This tumour was in close proximity to the spinal nerves and was continuous through the fourth cervical intervertebral foramen by a broad pedicle to a further extension of the growth in the form of a rounded mass about 4 cm. in diameter (Fig. 3), which lay just anterior to the lateral spinous processes, giving rise to a well-defined dumb-bell-shaped tumour. This latter portion of the tumour corresponded in position to the palpable mass in the neck which was detected clinically.

In the heart there were subendocardial hæmorrhages in the left ventricle. The air passages were filled with dark, blood-stained fluid and the lower lobe of the right lung was dark red, consolidated, and airless, portions of the affected lobe sinking in water.

Histology.—The tumour destroying the pineal gland had the microscopic structure of a pinealoma of the adult type, being composed of the two kinds of cells normally found in the fully developed pineal gland. Figs. 4 and 5 demonstrate these features.

The cervical tumour closely resembled the pineal growth. The two distinct cell types were present (Fig. 6), the larger having vesicular nuclei and pale cytoplasm and the smaller dark-staining nuclei closely resembling lymphocytes. These latter cells were mainly in broad trabeculæ of loosely knit connective tissue which supported the thin-walled blood vessels. The large nuclei were rather more pleomorphic than in the pineal tumour and more of the small dark cells were lying free amongst the larger type than in the pineal tumour, in which the small cells were mostly confined to the trabeculæ (Fig. 5). A section of the pedicle of the tumour (Fig. 7) showed that there was infiltration within the sheath of the spinal nerve as well as alongside it.

Careful macroscopic dissection and multiple histological examinations failed to reveal any other tumour deposits in the neuraxis or its membranes.

The consolidated portion of the right lung showed advanced hypostatic pneumonia.

Discussion

The clinical course of the disease and the physical findings led to the diagnosis of a dumb-bell tumour in the cervical region causing spinal-cord compression. Laminectomy was undertaken as an emergency procedure because of sudden respiratory failure. During the illness there were no signs or symptoms which suggested the presence of the primary lesion in the pineal region.

At the time of the operation histological examination of a piece of spinal tumour by frozen section did not lead to the correct diagnosis. Large cells with vesicular nuclei were seen, together with what were taken to be lymphocytes, and the appearance was thought to suggest a reticulum cell sarcoma although it was realized that the site was unusual. After the true nature of the lesion had been discovered at autopsy and the frozen section re-examined, it had to be admitted that the correct diagnosis might well have been made had it been considered in the differential diagnosis at the time.

Globus and Silbert (1931) have described pineal rests in the quadrigemminal plate, and Russell (1944) two cases with rests in the infundibular region, but no mention of them can be found in the spinal cord. It may be possible for the spinal tumour in this case

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FIG. 1.—The medial aspect of the right cerebral hemisphere. The pinealoma cut in the saggital plane can be seen as a mottled greyish tumour in the position normally occupied by the pineal gland.

FIG. 2.—The cervical cord from the dorsal aspect. The cord is compressed by the tumour, most of which can be seen to be intradural. The pale oval extradural portion is the cut pedicle which passed through the intervertebral foramen of the fourth cervical nerve.

FIG. 3.—The anterior aspect of the extramedullary portion of the cervical tumour. The pedicle of the tumour emerging from the intervertebral foramen of the fourth cervical nerve can be seen. The neighbouring spinal nerves have been dissected out, except the fourth cervical, which is incorporated in the pedicle.

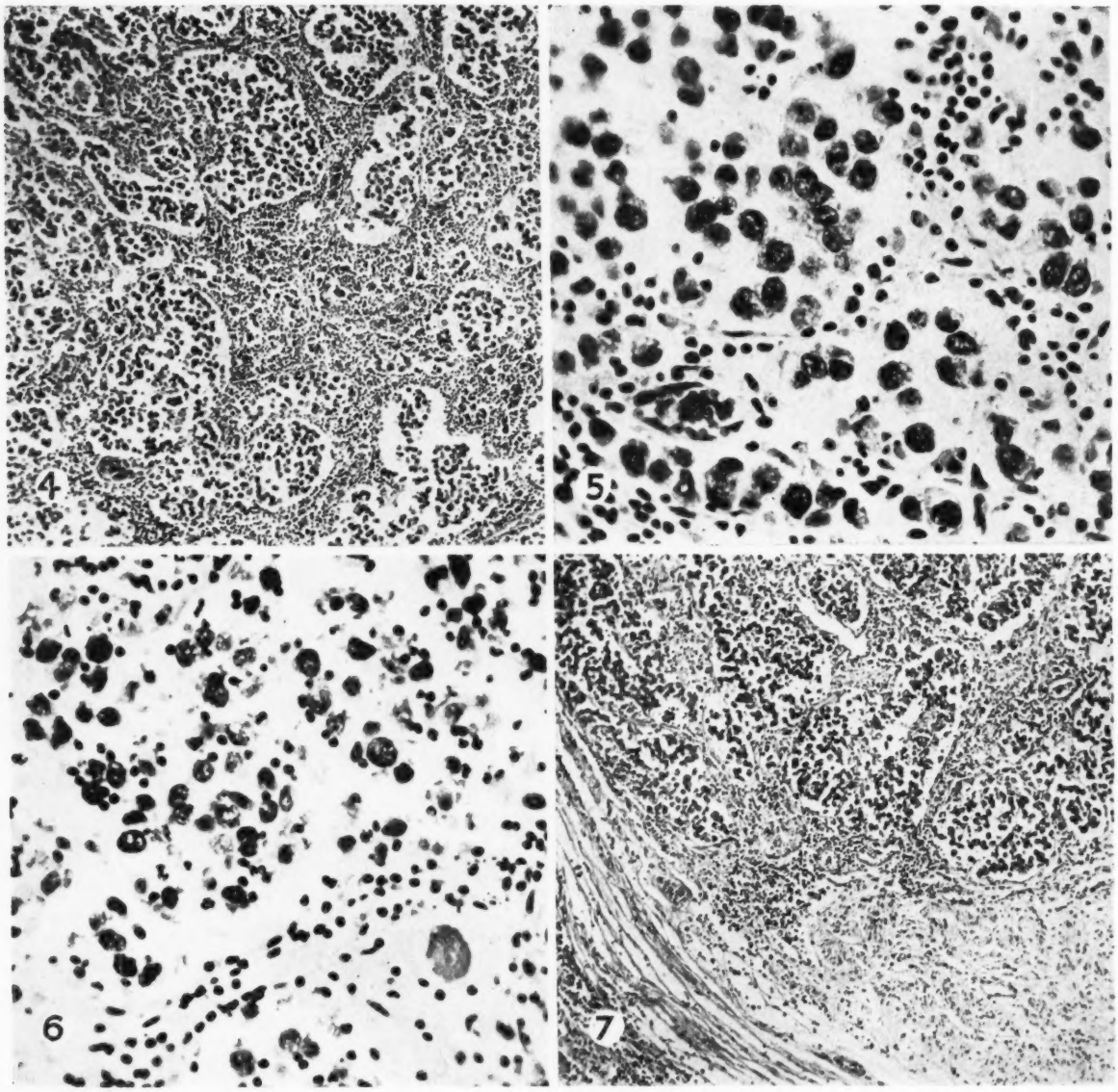

FIG. 4.—A low-power photomicrograph of the pineal tumour to show the typical structure of a pinealoma (Hæmalum and eosin, ×65).

FIG. 5.—The same as Fig. 4 but at a higher magnification. The large parenchyma cells are lying in groups surrounded by delicate connective tissue in which are the smaller darkly staining cells and blood vessels (×320).

FIG. 6.—A photomicrograph of the spinal tumour to show the similarity to Fig. 5. The parenchyma cells are slightly more pleomorphic and there are more small dark cells lying free amongst the larger cells (× 320).

FIG. 7.—A section through the pedicle of the spinal tumour to show invasion along the nerve, both within the sheath and outside it. The sheath can be seen on the left, and part of the surviving nerve in the lower right corner (×65).

to have arisen from a rest, but the presence of a true pinealoma as well makes it almost certain that the cervical tumour was a metastasis from the primary tumour in the brain.

Summary

A case of pinealoma with a solitary spinal metastatis causing cord compression and forming a dumb-bell tumour is described.

The primary tumour gave no clinical signs or symptoms and was discovered only at necropsy.

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HYSTERIA IN ONE OF A PAIR OF IDENTICAL TWINS

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Introduction

Although there exist in the literature a large number of papers of a psychological nature dealing with twins, most of these have been reports on single pairs of twins which, as Luxenburger (1930a) has shown, are largely useless for statistical purposes. Granted that monozygotic, identical twins (as opposed to dizygotic twins) have the same hereditary equipment, an assumption which is now considered to be fully justified in practice if not in theory, it is clearly necessary to compare suitable series of monozygotic and dizygotic twins in attempting to assess the relative importance of inherited and environmental factors responsible for psychological disorder such as hysteria. Furthermore, as Slater (1938) has pointed out, it is essential to take care that in any such series the numbers of the two types of twins are comparable with their proportional representation in nature. In this connexion the table compiled from the literature prior to 1930 by Luxenburger (1930b) is interesting, for of the nine pairs of twins showing a psychopathic personality and hysteria described, all were uniovular and none binovular—a state of affairs which militates against their being of much statistical value.

This report, then, cannot be regarded as a contribution to the solution of the problem of the relative importance of environment and heredity in the causation of hysterical illness. Nevertheless pairs of discordant uniovular twins are of exceptional significance in elucidating the nature of pathogenic factors of an environmental kind; the parallel history of an individual of like constitution who has remained well provides a chance of putting one's finger on those experiences in the life of the patient which have proved critical in the development of the illness. Part of the interest of the case described below is the suggestion it provides that the twin situation itself may play this role.

Case History of the Twins

Family History.—The father of the twins is a nervous, irritable man of fifty-three. Before his marriage he is said to have been "shell-shocked" in France, and his wife recalls that in the early days of their marriage he frequently cried like a woman and hid at the bottom of the bed when frightened or distressed. He is at present employed as a jobbing gardener. The twins' mother, who married their father thirty-one years ago, is a stable, hard-working woman who adopts a sensible attitude to her children and to her husband. She has been married twice; by her first marriage she had two children, who are now thirty-five and thirty-three years old, and by her present husband she has had nine children, all of whom are living.

The twins then have a stepbrother and sister, an elder sister of twenty-seven years of age, two younger brothers and four younger sisters ranging in age from twenty-five to fourteen. Of these, only one brother, now twenty-two, is described as being in any way nervous. This youth as a child was forbidden to play games on account of a supposedly weak heart; nevertheless, he was called up into the infantry and served overseas until he was invalided home on psychiatric grounds. He broke down after witnessing a harrowing massacre of civilians; subsequently he was apparently "unable to walk" and frequently burst into tears. He is now in regular employment as a storeman, has married, and is apparently much less nervous than hitherto.

The only family history obtained of other multiple pregnancies is that of a paternal uncle, who has twin sons; it is not known whether they bear a close resemblance to each other.

Personal History of the Twins.—Anne and Betty were born twenty-six years ago, Betty being stronger at birth than Anne, who is the subject of this report. Betty, who then weighed 3 lb. more than Anne was breast-fed because she made more of an effort to get milk in contradistinction to Anne, who was reared on the bottle. Nevertheless both apparently were well in infancy and childhood, and grew up to be strong, healthy girls. Both twins were backward at school, and the educational authorities at one time suggested sending them to a special school, although their mother would not countenance this step. They were both good at handiwork, embroidery, toy-making, and the like, but on her own admission Anne was scarcely able to read properly on leaving school at fourteen.

The twins were very much attached to each other, and were apparently inseparable until they left school. Both until then had the same interests and pursuits, and needed no other friends. Nevertheless, Betty was always the pet twin with her family, and it was she who usually took the initiative in organizing their games. When they reached their fourteenth year, however, Betty began to show considerable interest in the opposite sex, to Anne's displeasure, for she tried to prevent her sister from selecting a boy friend at this time, telling her that she did not need any friends other than herself; she was, however, unsuccessful in the attempt. Anne, unlike Betty, showed little interest in boys, and devoted much of her spare time to gardening, tending pet animals, and joining in Girl Guide activities.

After they left school, both twins went to work for a year in a laundry, working side by side. They both left on the same day after Anne had found the work too arduous, and sought domestic employment, finding work in neighbouring houses. Both continued in this work until they were sixteen years old.

History of Anne's Illness.—At the age of sixteen, Anne was taken ill with jaundice whilst at a summer Rangers' camp. She was sent home, and although her icterus cleared fairly quickly, she apparently had marked anorexia for some seven weeks. She then returned to her domestic duties, although for the next three or four months she felt continuously ill and drowsy, even falling asleep at the meal table. Her drowsiness increased, and at length she was admitted to hospital (some nine years ago) complaining in addition of backache and pains in her limbs. The hospital records state that although apyrexial on admission, she was very drowsy, especially in the daytime ; she was noted to have sluggish pupillary reactions to light, and exaggerated knee jerks, whilst an ophthalmologist reported low-grade bilateral optic neuritis. A lumbar puncture revealed a normal cerebro-spinal fluid save for the presence of 8 cells per c.mm., their nature not being specified, and 50 mg. of protein per 100 c.cm. She was diagnosed as having acute encephalitis lethargica and was transferred after five weeks to an Isolation hospital where she was detained for a further five months.

Within a few months Anne developed marked weakness of her left arm and leg, whilst both hands became very shaky and tremulous. On one occasion, following a hearty slap on the back (administered probably in reproof) she is said to have lost consciousness suddenly and to have remained in this state for a considerable time. Subsequently she developed occasional spasms of her back with jerking movements of her left leg when she attempted to walk. It was also noticed that any sudden noise or start might precipitate a screaming and crying bout. Subsequently she was transferred to a third hospital, where she was treated as an in patient for a further eighteen months. Despite intensive physiotherapy she made little progress, until one day when the power suddenly returned to her limbs in a matter of a very few minutes. She was then discharged home ; the diagnosis on discharge being " psychoneurosis with functional paralysis of the legs." Her mother recalls that at this time she was able to get about fairly well except for slight weakness in her arms and legs. At this time too, she started to wear masculine dress and to crop her hair short ; in explanation, Anne said that she wore trousers to cover her thin legs and kept her hair short as she had difficulty in lifting her arms to dress her own hair.

Soon after Anne's return home, the family was evacuated to the west country, and whilst there Anne had a relapse. She was then supplied with special corsets and a caliper for her left leg ; these she wore until four years ago, when they were given up on the advice of an orthopædic specialist. By this time her family had returned to their own home, so she was able to attend her local hospital where she was given regular physiotherapy. Her condition improved slowly and though she had temporary relapses from time to time she was able to get about fairly well until four months before admission to this hospital, when, on hearing of the sudden death of a friend, she became suddenly unable to walk once more and took to her bed for a while. Latterly she has been hobbling about with the aid of two sticks. She has also complained of numerous attacks of faintness and loss of consciousness over the last two years, although her practitioner who has seen her in such attacks was not convinced that they were organic in nature.

During the last nine years the patient has not been in regular employment ; from time to time she has made a little money by breeding rabbits and selling plants. Her mother has stated that although she frequently expressed her desire to become independent of family support, whenever regular work was suggested she stated that she did not want to take up anything if she was not going to be able to carry on. Her interests and hobbies have continued to be largely concerned with gardening, the keeping of pets, and the Girl Guides ; to date she has apparently taken little interest in men.

Betty's Past History.—When Anne was taken ill at sixteen, her sister gave up domestic work and took employment as a waitress. At this age she first became engaged to a youth although she broke off the engagement on her own account. Soon afterwards she met her present husband, marrying him when eighteen. She gave up her work some six weeks before the wedding, as she felt run down, had lost her appetite, and complained of frequent headaches with insomnia. However, she apparently recovered her health before the wedding day and remained well until about three months before examination. Since then she has felt tired and run down, and has lost weight, but it appears that she is keeping house for her husband and six-year old daughter in difficult circumstances. She has carried on with her duties, however, and has not broken down at any time since her marriage.

Findings on Examination.—Anne, on admission to the National Hospital, Queen Square, in November, 1947, was found to be a rather thin but well-proportioned girl, who presented herself in masculine clothes, wearing a shirt and tie, long trousers, and sports jacket ; her hair was cut short and brushed in a male style. Her performance on simple initial intelligence tests suggested a low level of intelligence, but in addition her answers strongly suggested an hysterical attitude to the tests ; thus a characteristic answer was, " I don't seem to get on with that—I go all blanky." She appeared to be somewhat shy, depressed, and apathetic, but she was quite co-operative and well behaved.

Physical examination revealed no abnormality whatever in her general systems or in her central nervous system, and although her lower limbs were seemingly very weak no wasting or alteration in tone was demonstrable, whilst all the muscle groups involved contracted vigorously as antagonists and synergists. Her gait was frankly hysterical, and although she seemed unable to walk without the support of two sticks, when these were removed she was able to avoid hurting herself when she fell.

Ancillary investigations gave negative findings ; thus no radiological abnormality was detected in her chest, lumbar spine, pelvis, or skull ; an electro-encephalogram and a glucose tolerance curve were likewise normal.

Betty on the other hand looked in fair health. On examination no physical abnormalities were detected.

A Comparison of Physical Features.—A comparison of the physical features of the twins revealed a distinct difference in general appearance, although no doubt could be entertained but that they are identical twins. Betty, a healthy young woman of feminine build and appearance, was well developed ; she was 63 inches in height and weighed 8 st. 7 lb. Anne, on the other hand,

TABLE I

ANALYSIS OF FINGER PRINTS OF TWINS

Fingers :		1	2	3	4	5
Anne	R.	UL. 13·0	W. 21·20	W. 18·25	W. 23·16	UL. 19·0
	L.	UL. 17·0	W. 15·19	DL. 15·10	W. 21·14	UL. 19·0
Betty	R.	UL. 16·0	W. 16·22	W. 19·25	W. 28·20	UL. 16·0
	L.	DL. 14·3	W. 14·17	DL. 21·18	W. 24·20	UL. 19·0

looked definitely more masculine ; her face was thinner, her hips narrower, and she maintained a slightly kyphotic stance in comparison with her healthy twin's more upright posture. She was three inches shorter, and weighed 17½ lb. less than Betty. Nevertheless in regard to the texture and colour of their hair, eyelashes, and eyebrows, the colour of their eyes and the iris pattern, and also the shape of the ears, mouths, and hands, a striking similarity obtained. Apart from the difference in build and appearance noted above, no points of discrepancy of any degree were found.

Their blood groups were both Group O, Rh-positive, whilst their electro-encephalographic report was, " Records made on these patients were normal and identical, showing a symmetrical alpha rhythm of ten a second." In addition they both gave similar responses to the phenylthiocarbamide test for taste and smell.

Finally, a comparison of their finger prints showed the pattern types and ridge counts (counts to radial triradius given first ; W=whorl ; DL=double loop ; UL=ulnar loop) given in Table I. The prints show a closer similarity between the twins than between their right and left sides. The Anne-Betty product-moment correlation coefficient is +0·86 ; the right-left correlation coefficient is +0·80.

Intellectual Capacity.—A comparison of the intellectual capacity of the twins, tested on a variety of intellectual tests, gave the results in Table II. It will be seen from

TABLE II

COMPARISON OF INTELLIGENCE TESTS ON THE TWINS

Test	Anne	Betty
Wechsler Bellevue :		
Verbal I.Q.	78	86
Performance I.Q.	92	102
I.Q. Whale Test	83	93
Matrices :		
Score	28	23
Percentile	10th	5th
Grade	IV	V
Koh's Blocks :		
Score	72	78
Mental Age	13·9	14·2
Category (Benton's Scale)	High average	High average
Reading and Spelling Age :	6 years	6½ years

the above results that performance test scores were superior to verbal ; tests involving school-learning in particular were but poorly performed. Both twins were clearly below normal intelligence, but they did not sink into the category of mental defectives ; Betty's performance was slightly better than Anne's in most of the tests, but, despite individual variations, in no test did their scores differ by more than 10 per cent.

In view of Anne's assumption of male attire both twins were tested on the selective vocabulary test devised by Slater (1944). Anne scored successes with five masculine and seven feminine words, falling into the ninety-second percentile for women and showing a shift towards the male side. Betty did better, falling into the seventy-fifth percentile with six masculine and thirteen feminine words, but even this result is a little towards the male side. It is interesting to note that both sisters showed a remarkable resemblance with some attempts at definition. Thus, both women thought that the word " dragoon " had something to do with Africa, that " dovetail " was a bird, and that " kerosene " was a seed.

After preliminary investigation in this hospital, Anne was treated with intensive daily physiotherapy, whilst she also attended Dr. Debenham regularly for psychotherapy. As a result she made slow but steady improvement and on her discharge home after two months in hospital, she was walking well without the aid of support ; in addition she had ceased to show the short periods of hysterical mutism and " faints " which were a feature of her past history and which were in evidence on admission. She has been seen on several occasions since she left hospital and her condition has not noticeably changed.

Discussion

It was very evident that when admitted to this hospital Anne was a pure hysteric, no evidence of any underlying organic disorder being found. However, it can hardly be doubted that the attack of infective hepatitis she sustained ten years ago might well have rendered her physically ill for several months and might have accounted in some measure for her curious state on admission to hospital nine years ago. Nevertheless within a few months she had developed symptoms which seem to have been largely functional in nature, anticipating the development of a florid hysterical state. In passing one might mention that although detailed information is not available on this point, it now seems hardly likely that she was suffering from acute encephalitis lethargica when admitted to hospital at the age of sixteen, although the true nature of her disease at that time is not now apparent.

Our subject then developed overt hysterical

symptoms some time after sustaining an infection constituting a definite physical handicap, which, operating over several months, prevented her from enjoying many activities in her twin sister's company. It should be recalled, too, that this took place at a time when Betty had already started to seek the company of the opposite sex, breaking away from their previously exclusive twin friendship, a rift which Anne had unavailingly attempted to prevent. Furthermore, it seems that Anne, the smaller and weaker twin at birth, had always been more dependent on her sister, for it was Betty, the family favourite, who usually took the initiative. In this way a situation developed which might well have precipitated Anne's hysterical breakdown. A somewhat similar state of affairs was described by Newell (1930), in which one of a pair of identical twins reared together acquired an acute infection (thought to have been either acute poliomyelitis or an acute encephalitis) at the age of two, following which her physical development was retarded. When the twins were examined at fourteen years of age, the affected twin was found to be a highly strung, nervous girl, who felt herself to be, and indeed was, physically, intellectually, and socially inferior to her twin, of whom she had become inordinately jealous. Newell concluded that these psychological differences were more likely due to the handicap provided by physical disease than to any inherited difference or to environmental factors common to the twins.

An interesting feature shown by the case under discussion was that Anne preferred to wear masculine attire, although it is of note that even when she discarded such clothes she had a more masculine build and appearance than her twin. This difference between the two sisters was supported in some measure by their responses to Slater's selective vocabulary test, and, as noted above, Anne in her answers showed more of a shift to the male side than did her healthy twin. Her mother states that she first began to wear male attire when she left hospital seven years before, and that she maintained in explanation that trousers concealed the thinness of her lower limbs and that a masculine hair style was easier for one in her enfeebled state to manage.

It is perhaps not too fanciful to suppose, however, that her liking for male clothing was in part motivated by a subconscious desire to maintain Betty's exclusive companionship at a time when she had not herself developed the heterosexual proclivities shown by her healthy twin.

That identical twins may show marked differences in psychosexual development even when brought up together has been noted before, and Cronin (1933) in an extensive psychoanalytical study described such a pair, although his conclusions are not germane to our study and need not therefore be discussed.

When identical twins are brought up together and come under the same environmental influences at the same time, they will naturally grow more alike than they otherwise might be, and one might reasonably expect them to show by and large the same personality responses to any given situation. However, as Lange (1929) has shown, they may in fact develop in a polar direction—the one, for example, vain and unscrupulous, the other shy and conscience-stricken. He postulates that this may be due to a tendency for them to regard their qualities and faults as common possessions. Our pair, though strikingly similar in physical build and intellectual capacity, showed some evidence of this polarity. Thus Anne, is shy, retiring, over-dependent, and immature in her psychosexual development, whilst Betty is much more enterprising and self-reliant and at a normal age she sought to break away from her sister's exclusive company in favour of that of the opposite sex.

When an attempt is made to determine the cause of Anne's hysterical breakdown, it should be borne in mind that inherited factors are probably of considerable importance, as it will be recalled that both her father and one of her brothers have shown evidence of an unstable personality. Indeed, her healthy twin, though never having shown overt hysteria as far as is known, had to give up her work six weeks before her marriage on account of symptoms which had no apparent physical basis.

The problem presented by this pair of twins is, then, given that both are equally endowed by heredity with a hysterical potentiality, how it is that one of them has had a fairly normal career, with only a few weeks during which she showed a mild neurasthenic syndrome, while the other has suffered a chronic and almost completely incapacitating illness of nine years' duration, during which she has lived a dependent and parasitic life confined to her own home. We must suppose that the twins took a slightly different path very early in life. Owing to the fact that uniovular twins commonly share the same placental circulation, if either has a slight advantage over the other, that advantage is likely to become exaggerated. There are on the average greater differences in birth weight between uniovular than between binovular twins. Betty was born rather heavier than Anne and was more robust; as a consequence she was given the additional advantage of breast-feeding, of which Anne was deprived. We may suppose that Anne never caught up with her sister's lead, and as a result became more dependent on Betty than Betty

was on her. This again may well have led to the family's preferring Betty to Anne who accordingly took more and more a back seat.

The illness that Anne underwent at sixteen was probably of critical significance, and we must attribute to it the eventual considerable difference in physique between the twins. It may perhaps also have partly caused the greater retardation of development in intelligence in Anne's case. The slight difference between the twins also became critical in the psychosexual field. When Betty started to take a normal interest in the opposite sex at 14, Anne did not follow her lead but took the attitude of the rejected lover. According to Dr. Debenham, who undertook some psychotherapy for Anne and also had a number of interviews with Betty, both twins show some homosexual features in the psychological field, but in Anne's case they are more marked. Anne's development took an overtly homosexual form, as is shown by the style of dress she assumed, although it is not suggested that she has at any time engaged in homosexual practices.

Taking the illness from the psychodynamic point of view, we may say that Anne's hysteria was a true flight into illness when she found that, do what she could, she could no longer retain her old place in her twin's affections. This excessive attachment, common among uniovular twins but very rare between ordinary sibs or binovular twins, seems to have played a dominant role in the course of Anne's long illness ; if she had not been born a twin she might never have become an hysteric.

I wish to express my thanks to Dr. Margaret Ferguson for her psychometric assessment of the twins, to Dr. Debenham and to Dr. Elithorne for taking and comparing their finger prints. I am especially grateful to Dr. Eliot Slater for his help and encouragement in the preparation of this report. In addition, I have to thank the Medical Committee of the National Hospital for their permission to publish this case.

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BOOK REVIEWS

Studies from the Rockefeller Institute for Medical Research, Volumes 131 and 132. A Study of Nerve Physiology. By Rafael Lorente de Nó. 1947 : Rockefeller Institute for Medical Research, New York. Pp. 496 and 548. Price $2 each volume.

This monumental work marks yet another milestone in the rapidly evolving history of neurophysiology. Following his early contributions to neuro-anatomy, Rafael Lorente de Nó turned his attention to the detailed structure of the nervous system and produced his studies of the cyto-architecture of the cerebral cortex. This consideration of structure led him to investigate nerve cells functioning in groups, from which evolved his concepts of neuronal circuits and reverberatory systems recently developed by others into the theory of " feed-back " and " oscillator systems."

Finally, Lorente de Nó's enquiries narrowed down to the functions of neurones as individuals : and these two volumes embody the results of this work. Filled with details of hundreds of personal experiments, they also record the observations of nearly every student of neuronal function.

Firstly, a consideration of the effect of changes in the external environment upon the function of individual nerve fibres leads to important conclusions regarding the role of ionic balance and gaseous exchange in this function. Then follows a series of studies on the electrical properties of nerve, posed agains tthe physico-chemical background of the earlier chapters. These experiments were carried out on isolated frog nerve preparations, most of the studies consisting of the measurement of the changes in demarcation potential under varying physical and chemical conditions. Particular stress is laid on the properties of nerve fibres considered as core conductors, and upon polarization of nerve fibres, factors which have previously been given scant attention. From these results the author, in collaboration with Dr. L. Davis, proceeds to a mathematical analysis of his findings and the formulation of the properties of nerve in mathematical terms. This is of importance in forming an interesting corollary to the studies of workers such as Rachevsky, McCulloch, and Pitts.

The question of the role of acetycholine in nerve function is discussed at length. A nice balance is maintained between the rival schools of thought, the views of both Nachmansohn and his colleagues on the one hand, and of Gerard and of Eccles on the other, being presented against the background of Lorente de Nó's own fundamental experiments. But the principal theme of these volumes is the mutual interrelation which exists between intracellular metabolism on the one hand, and the electrical expression of that metabolism on the other : the studies detailed in this work bring us closer to an understanding of the causal relations between these two aspects of neuronal activity.

However, there are certain adverse features which, to the ordinary reader, will present great obstacles to

the understanding of these volumes. Thus the author has employed a special terminology in describing the details and the results of his experiments, and this has to be mastered before the work can be understood. In addition there is such a wealth of experimental minutiæ to unravel that, to anyone not engaged in similar laboratory studies, the principles emerging from experiment may be buried beneath a mass of detail. No neurophysiologist can, however, afford to overlook these volumes. As a record of unstinted personal endeavour and loyalty to the highest standards of scientific study, this work is almost unique. It will take its place, without doubt, as one of the classics of existing neurophysiology, and will point the way to further studies of the fundamental physical and chemical properties of nerve.

Clinical Examination of the Nervous System. By G. H. Monrad-Krohn. 1948. London: H. K. Lewis and Co. Ninth Edition. Pp. xx+459, with 131 illustrations. Price 16*s*.

The appearance of nine editions in twenty-seven years indicates the usefulness of this book to the student. There are, however, several features which are not entirely satisfactory. The book is too detailed for the beginner (over seventy reflexes are described), while the comments on disease and diagnosis which form a large part of it sometimes seem to be out of place.

Many of the illustrations are poor; others take up a whole page where a quarter of this space would have sufficed (for example, figs. 4, 5, and 6). An increase in the number of good illustrations would greatly add to the value of the book, while space could be provided by omitting much of the commentary. For example, two and a half pages are devoted to a "Short Survey of Pituitary Syndromes" but there are no illustrations of visual field charts.

The illustration of relatively simple tests, such as the examination of the ankle jerk, or of the voluntary power of the more important muscle groups, would be helpful to the student. The M.R.C. War Memorandum, No. 7 shows the possibility of illustrating clinical tests in a way that is worth considering when a book of this kind is being prepared.

Neurological Anatomy in Relation to Clinical Medicine. By A. Brodal. 1948. Oxford: Clarendon Press. Pp. 496+94 figures. Price 42*s*. (A revision and translation of "Neuro-Anatomie," published in Oslo.)

Knowledge of the anatomy and physiology of the nervous system is advancing so rapidly that many clinical neurologists find their knowledge of these subjects inaccurate and out of date. This readable book will help to bring the clinician up to date. The contents provide an outline of recent developments, and references are given which will provide more detail if this is required. Contrary to common belief, a better knowledge of anatomy will not necessarily make the clinician a better diagnostician. Many, however, feel that the practice of neurology is incomplete when it is merely a diagnostic and therapeutic exercise. Every clinical case should be scrutinized for the light it may cast on anatomy or physiology, and knowledge of recent anatomical discoveries is essential to such an approach. There is no doubt, therefore, that this book by Dr. Brodal will be welcomed by both physicians and students interested in neurology.

A Contribution to the Study of Sturge-Weber-Krabbe's Disease (Fourth Phakomatosis). By G. S. Philippopoulos. 1948. Athens. Pp. 128. Illustrated.

Out of four cases of Sturge-Weber-Krabbe's disease observed in Greece since 1934, three have been examined by the author and constitute the basis of the present thesis, written in Greek but containing a summary in English. In the third chapter special reference is made to the various clinical forms of the disease, including the bi-, tri-, and monosymptomatic forms, the *formes frustes* of French authors.

The disease or syndrome is a rare congenital developmental dysplasia, and by Jan van de Hoeve and his associates is claimed as a fourth division of their group of "phakomatoses." A very remarkable feature noted by the author in his first case is the presence of buphthalmus on the side *contralateral* to the side of the cerebral lesions. In the same case were: extensive (bilateral) facial nævus, prognathism of simian type, obesity, stunted body growth, and congenital hip dislocation. Against the use of the term "nævoid amentia" to include all cases of the disease is the fact that in the author's second case there is no amentia, the child being of exceptionally good intelligence though subject to very frequent transient minor epileptic attacks. In the third case intense periodic hyperæmia of the ear on the angiomatous side of the face is a hitherto unrecorded feature. Cutaneous telangiectatic and pigmentary lesions are present in a brother of the first patient as also in a brother of the third patient. The thesis constitutes a great contribution to the subject, and includes an extensive bibliography.

Epilepsies. By L. Marchand and J. de Ajuriaguerra. 1948. Paris: Desclée de Brouwer et cie. Pp. 724. Price 475 fr.

This important work will be invaluable, especially to younger neurologists who are largely ignorant of the many important contributions to the subject of thirty or more years ago. L. Marchand has devoted much of his life to the study of epilepsy, and this treatise represents not only the product of long clinical experience but also a most valuable collection of references. The authors show the zeal of the enthusiastic collector in amassing details of epileptic rarities both from their own clinics and also from the literature.

There are many sections of interest, including the effect of brain disease such as chorea on the epileptic; many remarkable examples of emotion precipitating a convulsion; epilepsy precipitated by stimulating an injured nerve or scar; urogenital epilepsy; and disorders of body image as an epileptic phenomenon. The psychological aspects of epilepsy are considered in great detail.

In some respects this book is not up-to-date. For example there is little attempt to correlate modern neurophysiological knowledge with the clinical facts, and there is no mention of recent American developments in the study and surgical treatment of traumatic epilepsy. These omissions, however, will not reduce the great welcome this book must have from those interested in epilepsy.

Sexual Disorders in the Male. By Kenneth Walker and Eric B. Strauss. 1948. London: Hamish Hamilton Medical Books. Pp. xiv plus 260. Price 15*s*.

This simple, sensible treatise on a subject of great importance in the everyday lives of many patients, by a surgeon and a psychiatrist both having unequalled

experience in this field, will be generally welcome. The discussion of the innumerable treatments that have at one or another time been tried for impotence is balanced and critical; and those methods which have proved valuable are related to their several indications in a way which gives their due significance to ætiology and diagnosis.

Introduction to Group-Analytic Psychotherapy. By S. H. Foulkes. 1948. London: Wm. Heinemann Medical Books Ltd. Pp. xiv plus 181. Price 21*s*.

It is not very easy to see why this book was published. It can be of no interest except to psychotherapists engaged in group therapy, and for them it can have little that is new. The author's main concern seems to be to persuade his fellow psychoanalysts that an analytic technique can be followed in the unfamiliar and heterodox setting of a group, and that worthwhile results and interesting findings can then be made. It does not seem likely that psychoanalysts in general now need any such persuasion. Psychoanalytic doctrine is itself presented as beyond all question; and the author's patronizing attitude to medicine and medical men and his tendency to self-gratulation do not add to the book's attractions.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Evolution of the Forebrain. By G. W. H. Schepers. 1948. Cape Town: Maskew Miller Ltd. Pp. 212. Illustrated. Price 50*s*.

Pathology of the Nervous System. By J. Henry Biggart. 1949. Edinburgh: E. and S. Livingstone. Pp. 352 with 232 illustrations and 10 colour plates. Second Edition. Price 21*s*.

Atlas of Peripheral Nerve Injuries. By William R. Lyons, Ph.D., and Barnes Woodhall, M.D. 1949. London and Philadelphia: W. B. Saunders. Pp. 339. Price 80*s*.

Observations on the Pathology of Hydrocephalus. By Dorothy Russell. 1949. Med. Res. Council Spec. Rep. Series No. 265. London: H.M. Stationery Office. Pp. 138. Illustrated. Price 6*s*.

Neuroradiology. By Alexander Orley. 1949. Oxford: Blackwell Scientific Publications Ltd. Pp. xii+421. Price 63*s*.

Mental Readjustment. By Sidonie Reiss. Translated from the German by Bernard Miall. 1949. London: Allen and Unwin. Pp. 167. Price 10*s*. 6*d*.

Man's Quest for Significance. By Lewis Way. 1949. London: George Allen and Unwin. Pp. 211. Price 12*s*. 6*d*.

Psycho-analysis Today. Edited by Sándor Lorand. 1949. London: George Allen and Unwin. Pp. xvi+404. Price 25*s*.

Psychological Medicine. By Desmond Curran and the late Eric Guttmann. Third Edition. 1949. Edinburgh: E. and S. Livingstone. Pp. viii+252. Price 12*s*. 6*d*.

How Psychiatry Helps. By Philip Polatin and Ellen C. Philtine. 1949. New York: Harper and Brothers. Pp. xii+242. Price $3.

Principles of Psychiatric Nursing. By Madelene Elliott Ingram. 1949. Philadelphia and London: W. B. Saunders Co. Third Edition. Pp. xvii+525. Illustrated. Price 19*s*.

Cybermetics: or Control and Communication in the Animal and the Machine. By Norbert Wiener. 1948. New York: John Wiley and Sons Inc. London: Chapman and Hall. Pp. 194. Price 18*s*. or $3.

Le Cortex Cérébral: Etude Neuro-Psychopathologique. By J. de Ajuriaguerra and H. Hécaen. 1949. Paris: Masson et Cie. Pp. viii+413. Illustrated. Price 1250 fr.

Verstehende Psychologie (ein Lehrbuch). By Hans W. Gruhle. 1948. Stuttgart: Georg Thieme Verlag. Pp. xi+622. Price DM30.

Die Synkopalen Anfälle. By Walter Schulte. Second Edition. 1948. Stuttgart: Georg Thieme Verlag. Pp. viii+92. Price DM9.60.

Untersuchungen aus dem Grenzgebeit zwischen Psychopathologie und Endokrinologie. By M. Bleuler and others. 1948. *Archiv für Psychiatrie und Nervenkrenkheiten, Bund* 118–180 *and Zeitschrift für die gesamte Neurologie und Psychiatrie, Bund* 180. Berlin: Springer Verlag. Pp. 257. Price DM24.

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RAPID SERIAL ANGIOGRAPHY: PRELIMINARY REPORT

BY

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Egas Moniz (1927) originated the method of visualizing the cerebral arteries in the living human by radiography of an injected radio-opaque substance. In addition he has been associated with many subsequent advances. According to Sanchez-Perez (1941) the first phlebogram was obtained by Egas Moniz on Dec. 19, 1931, accidentally from a technical error in making a late exposure. Moniz was quick to realize its implications and from this time angiography, which is the visualization of both arteries and veins, may be said to have replaced arteriography. The practice of making repeated exposures during an injection was then developed, and by 1934 the Portuguese school had elaborated the technique of taking six films in six seconds at one-second intervals (Egas Moniz, Lima, and Caldas, 1934). The apparatus used, called the "radio-carousel," consisted of a circular table on which six cassettes were fixed equidistantly. Mechanical rotation of the table brought the cassettes into position for serial exposure. By this means they were able to make crude studies of the cerebral circulation (Egas Moniz, 1934), and little has been added to their findings since that time.

The value of phlebograms in addition to arteriograms is now well established. For routine work most centres gradually evolved simple mechanical contrivances enabling two, three, or more films to be exposed over a period of about four to six seconds (Sanchez-Perez, 1943; Engeset, 1944; Lindgren, 1947; Boardman and Vickers, 1947). Such methods, satisfactory for routine diagnostic use, are subject to the criticism that they give pictures representing only isolated parts of a cycle of events. A study of the full circulation was not possible, and on these isolated pictures some unwarranted conclusions have been reached in reference to variations in circulation rate, the filling of vessels, arterial spasm, and even blockage.

Further development was possible along two lines.

Cineradiography depended on a cinematographic record of the image projected on a fluorescent screen. Holm (1944) first reported its use in cerebral angiography. However, by this method at present there is great loss of definition. Lysholm and his assistants (1947) were fully aware of this drawback, and sought improvements in the definitive quality of the fluorescent screen and in the lens system of the camera.

Rapid Serial Exposures.—An alternative approach to the problem was by means of rapid serial exposures on a length of *x*-ray film. It was felt that this method could provide clearer pictures although the sensation of movement would be sacrificed. Exposures at a rate of up to two per second would then be adequate, at this stage, to study changes in the circulation, provided that the full period of the circulation could be covered. This paper is concerned with the results obtained by means of an apparatus developed along these lines.

Apparatus

Only a brief account of the apparatus will be given here. A prerequisite to its design and construction was *x*-ray equipment with the following characteristics:

1. An *x*-ray tube of the requisite power output with sufficient heat capacity to enable it to withstand exposures at half-second intervals over a period of 10 to 15 secs.

2. Film and intensifying screens which, used in combination with such a tube, would give sufficient penetration of the skull to obtain a clear image with an exposure as short as 1/5 sec.

A Machlett Dynamax, Type D, rotating anode fine focus *x*-ray tube, Kodak ultra-speed intensifying screens, and Ilford's Red Seal film were found to be suitable.

It was decided that the machine would need to fulfil the following requirements:

1. The size of each image should be 10 in. wide by 8 in. long, as this was the minimum size necessary to obtain a picture of the cerebral vascular tree.

2. It should be capable of taking twenty-five successive images entailing a total length of film of about 20 ft. This would cover adequately possible variations in the circulation time.

3. It should have three available rates of exposure: two per sec., three in 2 secs., one per sec.

* Nuffield Dominions Scholar from the University of Melbourne.

4. There should be a mechanism for the opposition of intensifying screens to the film at the time of exposure, as this is essential to obtain the necessary definition with such a short exposure.

5. The film should stand vertically, as by this means lateral views could be taken with the head in the brow-up position. This would facilitate percutaneous arterial puncture and accurate positioning.

6. The machine should fit the standard Lysholm-Schönander skull table which was available to us.

The considerable problems arising from these requirements were brilliantly solved by Dr. E. Schuster, O.B.E., who designed and constructed a machine based on the following principles :

1. The movements are driven by a constant-speed electric motor.

2. The timing devices depend on electrical circuits.

3. The film is taken up on a spool which is rotated by a transmission rod. This is timed to engage, rotate, and disengage automatically between exposures.

4. The intensifying screens are clamped to, and disengaged from, the film before and after the exposure by a system of electro-magnets.

5. The electrical impulse to set off the exposure mechanism of the *x*-ray tube is synchronized with the movement of the film.

Difficulty was experienced in developing a strip of film 20 ft. long and 10 in. wide, but was overcome by utilizing the principle of the "spiral holder," used to develop the lengths of film used in aerial photography during the 1939–45 war. The holder was modified to take film 10 in. wide.

Results

The results obtained by this method are illustrated by the records obtained from the following cases.

Case 1.—The record of this case has been used to illustrate the appearances in a normal angiogram (Figs. 1 to 18).

A man aged 40 years was admitted to hospital on Jan. 27, 1949. One week before, after a shivering attack on the previous night, he suddenly developed right-sided headache, and this was followed by a fairly rapid and progressive left hemiparesis affecting the arm more than the leg. Examination showed also left-sided sensory loss of cortical type affecting mainly the hand. His blood pressure was 135/85 mm. Hg, and examination of the cardiovascular system revealed no abnormality.

During the ensuing month there was marked improvement. On March 2 a right-sided routine percutaneous angiogram showed non-filling of the main branches of the middle cerebral artery, and a diagnosis of thrombosis was made.

On March 4 a lateral serial angiogram was carried out on the healthy left side. The percutaneous method described by Lindgren (1947) was used with local anæsthesia and Omnopon-Scopolamine premedication. Twelve ml. of 35 per cent. diodone were injected, of which a residuum of 2 ml. remained in the tubing connexion, making a total of 10 ml. entering the artery. Twenty exposures were made at intervals of $\frac{2}{3}$ sec., the first exposure coinciding with the beginning of the injection. The tube was set at 150 MA and 85 kV and the exposure time was 0·2 sec.

Figs. 1 to 18 reproduce the exposures made in $11\frac{1}{3}$ secs. and the legends attached interpret the various stages of the circulation.

Case 2.—The following case illustrates the special value of this method in the diagnosis of a pathological circulation.

A girl (No. 95,121/48) aged 19 years had suffered from attacks since the age of 7 years. In these there was a transitory loss of consciousness preceded by a sensation of numbness in the left hand. Examination showed slight motor weakness and a slight sensory loss of the cortical type in the left hand. Otherwise there was no abnormality on clinical examination, and there was no evidence of cutaneous hæmangiomata. *X*-ray examination of the skull showed a patch of irregular calcification in the right parietal region (Fig. 19). Examination of the cerebrospinal fluid showed no abnormality.

On Jan. 21, 1949, a right lateral serial angiogram by percutaneous puncture of the internal carotid artery was carried out with the same technique as

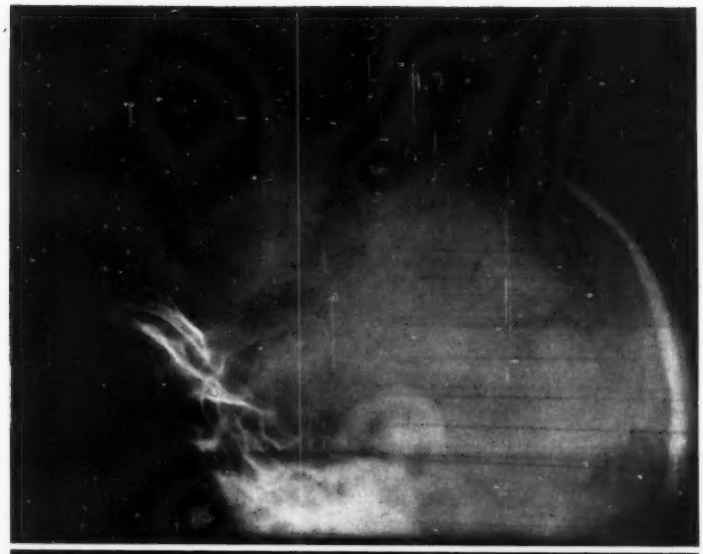
ILLUSTRATIONS

KEY TO LETTERING OF ARTERIES

Sy.	=	Carotid Syphon.
P.C.	=	Posterior Cerebral A.
A.C.	=	L or R Anterior Cerebral A.
F.P.	=	Fronto-Polar A.
Pre.Ro.	=	Pre-Rolandic or Candelabra. A.
P.P.	=	Posterior Parietal A.
P.T.	=	Posterior Temporal A.
A.A.	=	Artery of Angular Gyrus.
P.Cal.	=	Peri-Callosal A.
M.Cal.	=	Marginal Callosa A.

KEY TO LETTERING OF VEINS

I.L.S.	=	Inferior Longitudinal Sinus.
S.S.	=	Straight Sinus.
T.S.	=	Transverse Sinus.
G.V.G.	=	Great Vein of Galen.
I.C.V.	=	Internal Cerebral Vein.
B.V.	=	Basilar Vein.
V.L.	=	Inferior Anastomotic Vein of Labbé.
V.T.	=	Superior Anastomotic Vein of Trollard
S.P.S.	=	Spheno-Parietal Sinus.
V.A.	=	Ascending Vein.
S.V.	=	Sylvian Veins at " Venous crossroads."
Si.S	=	Sigmoid Sinus.



FIGS. 1 to 18.—Left angiogram to illustrate the normal appearances (Case 1).

FIG. 1 (at onset).—Left lateral view. There is no rotation in either plane, and centring is above and slightly behind the pituitary fossa.

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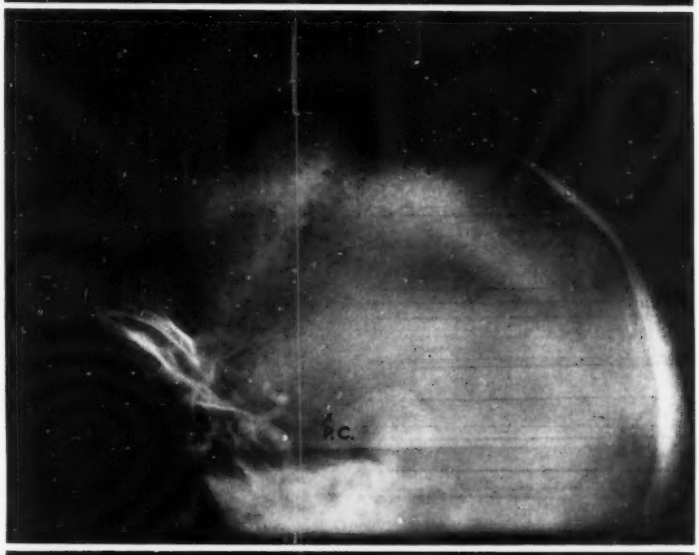

FIG. 2 (at $\frac{2}{3}$ sec.).—The diodone is seen faintly in the internal carotid and its branches. It has reached the genu of the anterior cerebral, the beginning of the ascending part of the middle cerebral in the sylvian fissure, and has filled the posterior communicating and the early part of the posterior cerebral (P.C.).

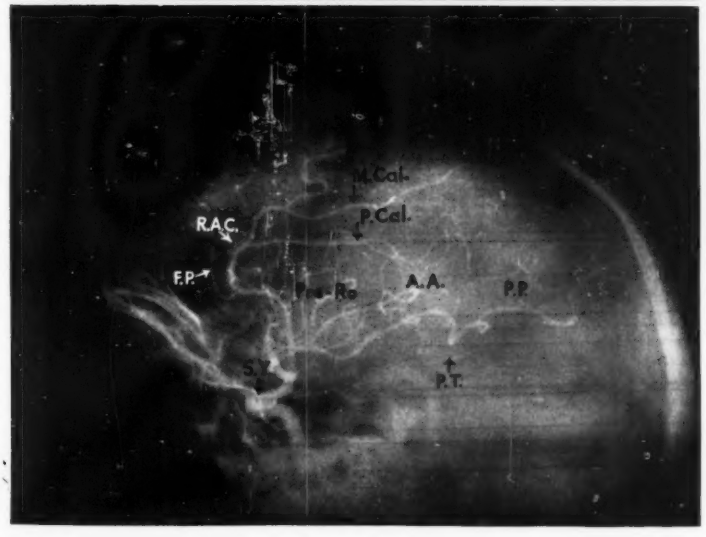

FIG. 3 (at $1\frac{1}{3}$ secs.).—There is filling to the periphery of the branches (P.Cal., M.Cal., F.P., Pre.Ro., P.P., A.A., and P.T.) of the anterior cerebral and middle cerebral arteries, with faint filling of the posterior communicating and posterior cerebral. The right anterior cerebral (R.A.C.) shows very faint filling indicating overflow to the opposite hemisphere. Anatomical variations are : (1) The carotid syphon (Sy.) has a " squashed " appearance ; (2) The early ascending portion of the anterior cerebral takes an unusual upward and backward course.

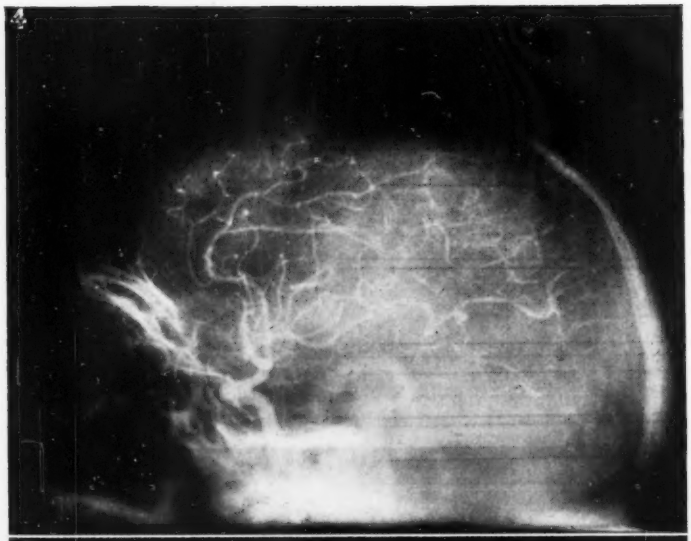

FIG. 4 (at 2·0 secs.).—The small unnamed branches have filled to the periphery. The diodone is now faint in the posterior cerebral (P.C.) and even fainter in the right anterior cerebral (R.A.C.). Diodone is still present in the internal carotid in the neck. In the usual angiographic procedure the first exposure would be made at about this stage.

FIG. 5 (at $2\frac{2}{3}$ secs.)—There is now no diodone in the internal carotid in the neck or in the region of the syphon. It is fainter in the proximal parts of the anterior and middle cerebrals. One may conclude that it has taken a little over 2·0 secs. and slightly under $2\frac{2}{3}$ secs. for the injection of 12 ml. of diodone. A diffuse cloudiness is now developing, indicating filling of the capillary bed. Careful comparison with Fig. 6 will show that the internal cerebral vein (I.C.V.), great vein of Galen (G.V.G.), and the posterior end of the inferior longitudinal sinus (I.L.S.) show very faint filling.

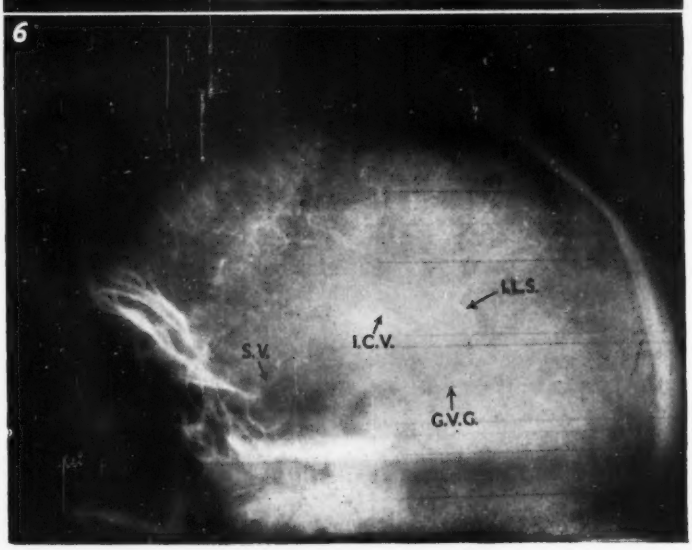

FIG. 6 (at $3\frac{1}{3}$ secs.).—The diffuse cloudiness is now marked. There are widely scattered very small vessels, and these are probably veins as they do not correspond with the peripheral small arteries shown in earlier exposures. The veins mentioned in Fig. 5 now show more definite filling. There is early venous filling at the Sylvian point (S.V.), and the sphenoparietal sinus (S.P.S.) is faintly filled.

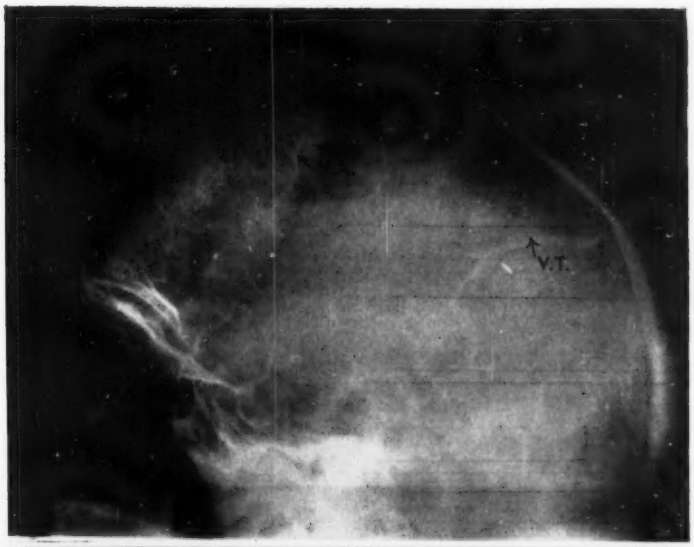

FIG. 7 (at 4·0 secs.).—More definite venous filling is seen and the capillary haze has commenced to clear. There are numerous superficial ascending veins (V.A.) in the frontal and parietal regions and faintly in the occipital region. One of these, larger than the rest, is at the posterior end of the parietal lobe and is probably the superior anastomotic vein of Trollard (V.T.). Proceeding backwards and downwards from the region where this vein arises, is another smaller vein which in later films is identified as the inferior anastomotic vein of Labbé (V.L.). The spheno-parietal sinus is more clearly seen. No basilar vein is seen. The usual first phlebogram taken 2 secs. after the arteriogram would show this picture.

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FIG. 8 (at 4⅔ secs.).—There are no new details but the veins previously mentioned show better filling and are clearer. It is seen that the anterior end of the internal cerebral vein (I.C.V.) curls back on itself.

FIG. 9 (at 5⅓ secs.).—The diffuse cloudiness due to the capillary haze has now almost gone. There is marked filling of the larger veins. No single Sylvian vein runs in the direction of the fissure of that name, and only a very small basilar vein (B.V.) can be made out. The small inferior anastomotic vein of Labbé is seen running into the transverse sinus (T.S.), and posterior to this there is an occipital ven.

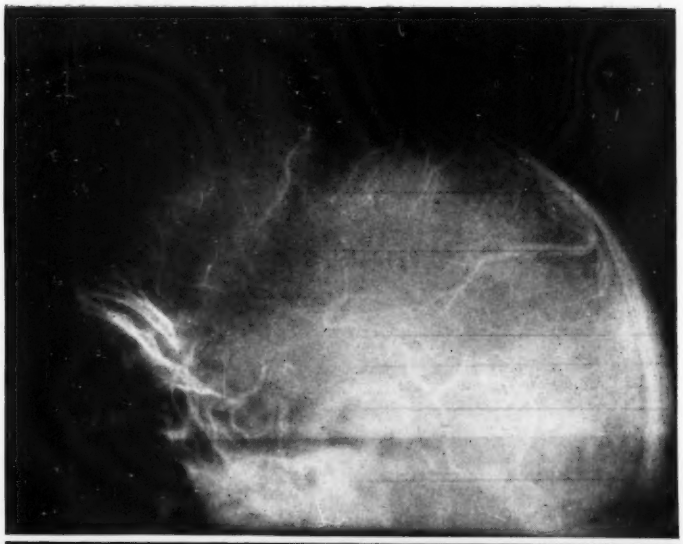


FIG. 10 (at 6·0 secs.).—There is marked filling of the large veins. In some clinics which take their second phlebogram 4 secs. after the arteriogram this picture would be seen. The structures can be identified from the labelling in the previous figures.

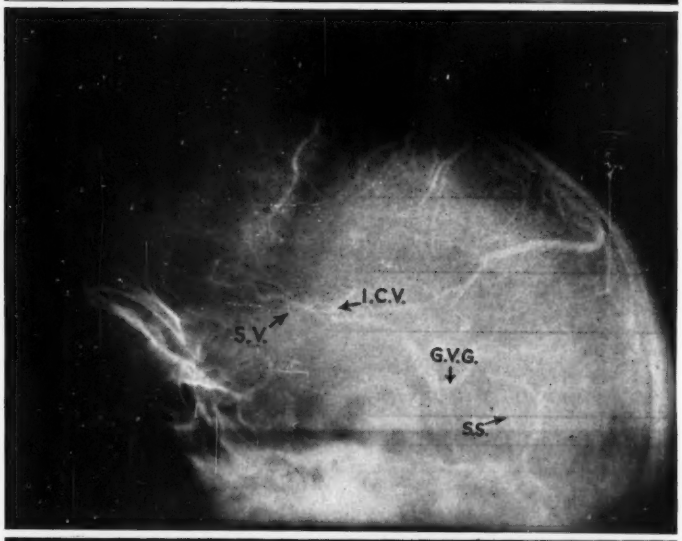


FIG. 11 (at $6\frac{2}{3}$ secs.).—This shows the maximal venous drainage. The superficial venous system is well seen and there is a full anastomosis of veins in the region of the Sylvian fissure (S.V.). Moniz called this the " venous crossroads." Arising from this region are the anastomotic veins of Trollard and Labbé and smaller veins passing down to the spheno-parietal sinus. Passing into this region is a vein from the frontal region. Do not confuse the superimposition of the shadows of these veins on the anterior end of the deep internal cerebral vein (I.C.V.) and its tributaries. The internal cerebral vein is clearly seen. It may be traced back to join the basilar vein to form the great vein of Galen (G.V.G.) which combines with the inferior longitudinal sinus to form the straight sinus, S.S.

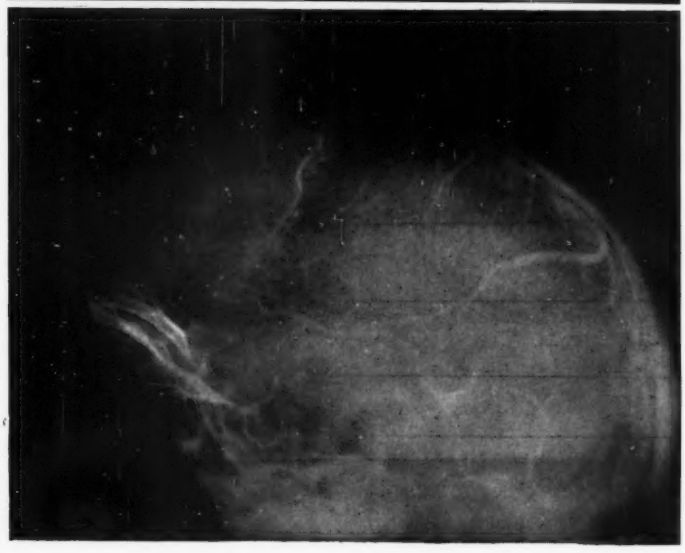


FIG. 12 (at $7\frac{1}{3}$ secs.).—This is a clear phlebogram.

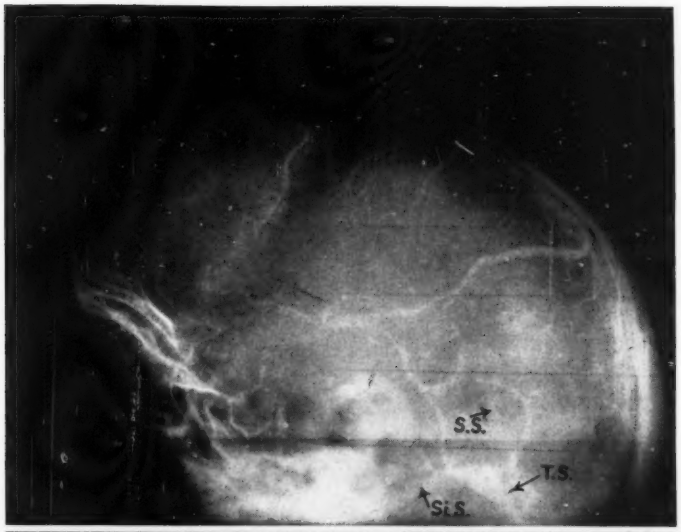


FIG. 13 (at 8·0 secs.).—There are signs of slight fading of diodone in the smaller veins. Where the second phlebogram is taken 6 seconds after the arteriogram, this picture would be seen. All the named veins stand out clearly. The superior longitudinal sinus, transverse sinus (T.S.), and sigmoid sinus (Si.S.) are well filled. The cavernous sinus cannot be made out with certainty.

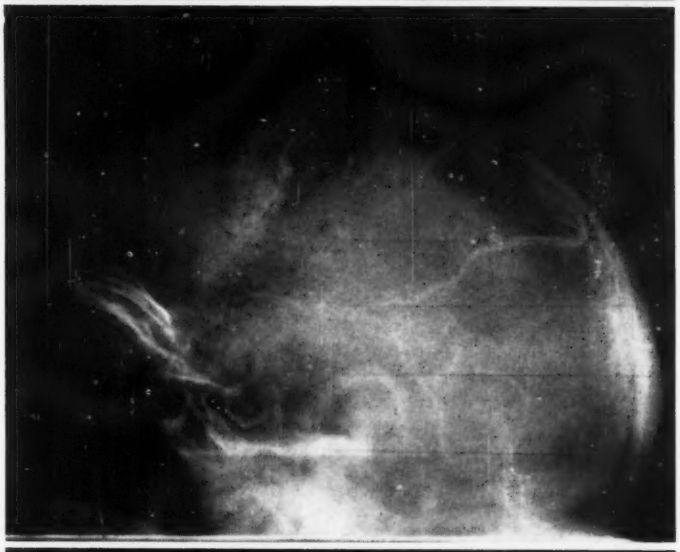


FIG. 14 (at 8⅔ secs.).—There are the first signs of fading of contrast in the larger veins. The spheno-parietal sinus is only faintly filled and the internal cerebral vein and great vein of Galen have faded a little. The inferior longitudinal and straight sinuses and the smaller veins have disappeared.

FIG. 15 (at 9⅓ secs.).—The fading is more marked. The venous drainage around the temporal lobe no longer shows. There are only a few frontal and parietal ascending veins.

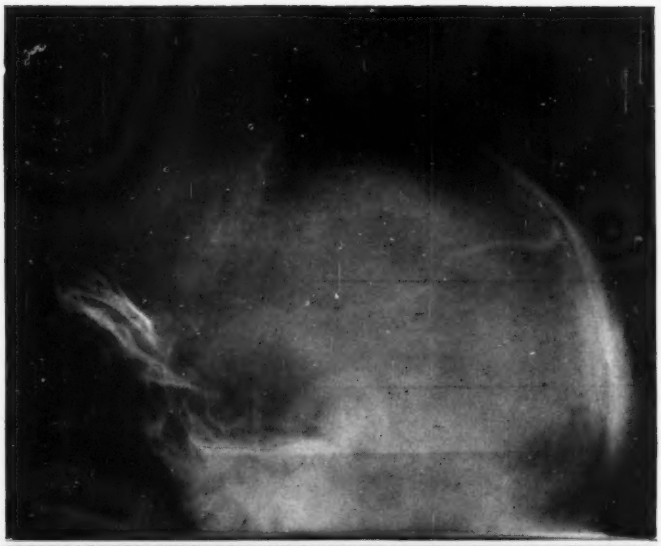
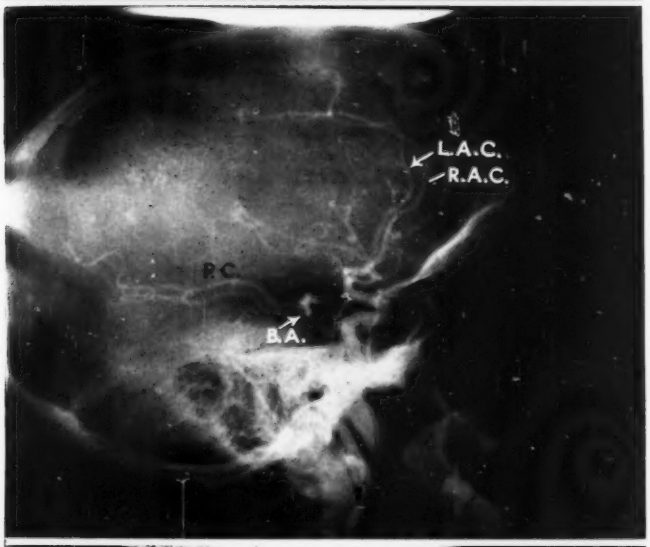
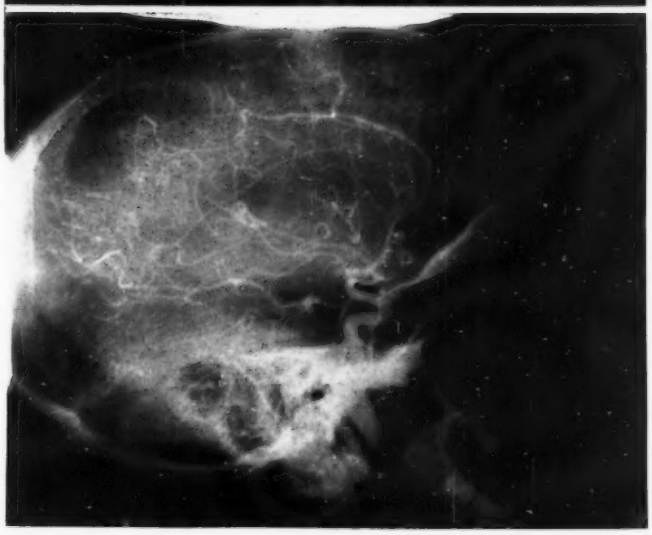


FIG. 16 (at 10·0 secs.).—There is further fading of the contrast.

FIG. 17 (at $10\frac{2}{3}$ secs.).—There is further fading.

FIG. 18 (at $11\frac{1}{3}$ secs.).—There is still very faint filling in some posterior frontal and parietal ascending veins. Exposure 19 at 12·0 secs. showed only the slightest trace of contrast, and exposure 20 showed no contrast.





FIGS. 19 to 34.—Right angiogram to illustrate an unusual type of angioma (Case 2).

FIG. 19 (at onset).—Right lateral view. There is no rotation in either plane and centring is in the region of the pituitary fossa. There is visible calcification in the right parietal region.

FIG. 20 (at $\frac{2}{3}$ sec.).—The contrast medium is seen in the following arteries: (1) internal carotid artery; (2) right and left anterior cerebral arteries (R.A.C. and L.A.C.); (3) The posterior communicating artery*; (4) right and left posterior cerebral arteries (P.C.). There is also slight but definite retrograde filling of the basilar artery (B.A.). The small vessels outlined beneath the posterior cerebrals are almost certainly the anterior superior cerebellar arteries. The anterior choroidal artery is also seen. The wider sweep of the right anterior cerebral may indicate some hydrocephalus on the right side, which is the side of the angiomatous malformation.

FIG. (21 at $1\frac{1}{3}$ secs.).—This is a full arteriogram and no abnormal vessel can be seen. The arteries are well filled with contrast to the periphery. The contrast is now fainter in the left anterior and posterior cerebral arteries. The main branches of the anterior cerebral artery and of the middle cerebral artery can be seen.

* It is a larger vessel than the posterior communicating seen in Figs. 2 and 3.

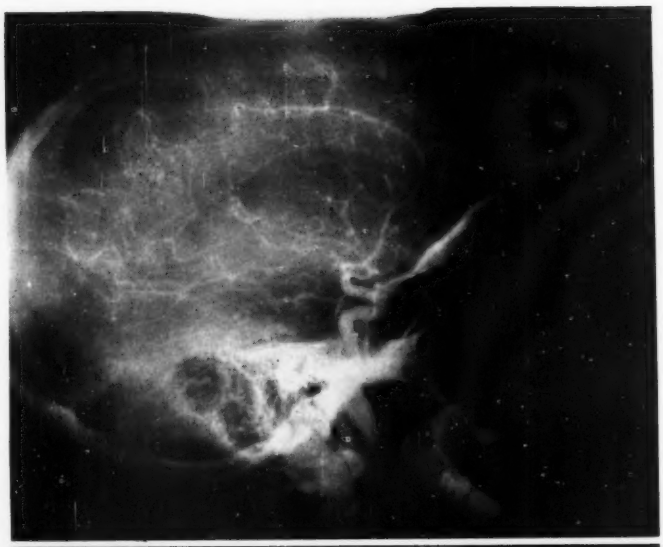


FIG. 22 (at 2·0 secs.).—This is a late arteriogram. It would be difficult now to detect contrast in the left anterior and posterior cerebral arteries. No abnormal vessels are seen, particularly in the region of calcification. The end of the column of diodone can be seen in the neck and it is missing in the next picture. Thus, the time of injection of the diodone was about 2 secs.

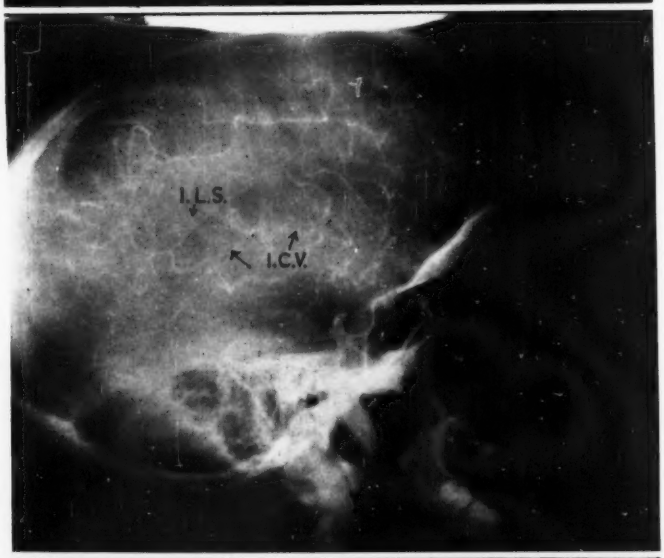


FIG. 23 (at 2⅔ secs.).—A diffuse cloudiness is now becoming evident. There is no diodone in the internal carotid or proximal arteries but there is still fairly good filling of the larger branches distally. The first veins can be distinguished if a careful comparison is made with Fig. 24 : the internal cerebral vein (I.C.V.) and the posterior end of the inferior longitudinal sinus (I.L.S.).

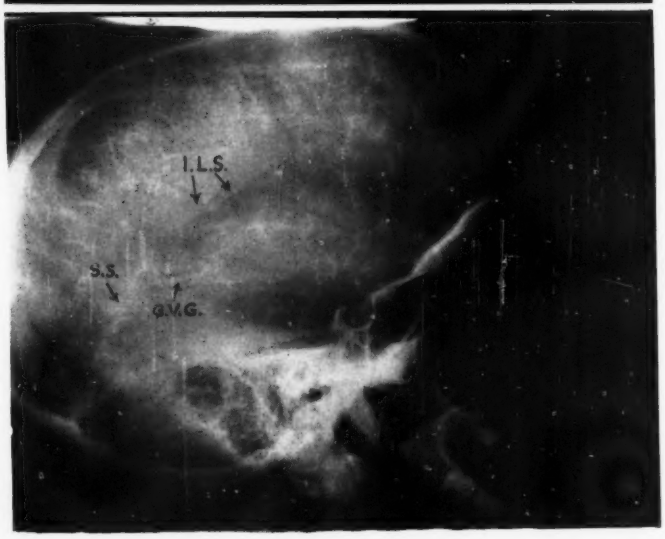


FIG. 24 (at 3⅓ secs.).—There is more definite venous filling. The inferior longitudinal sinus (I.L.S.), internal cerebral vein, great vein of Galen (G.V.G.), and straight sinus (S.S.) are seen. There is early venous filling at the Sylvian point and in the anterior temporal region.

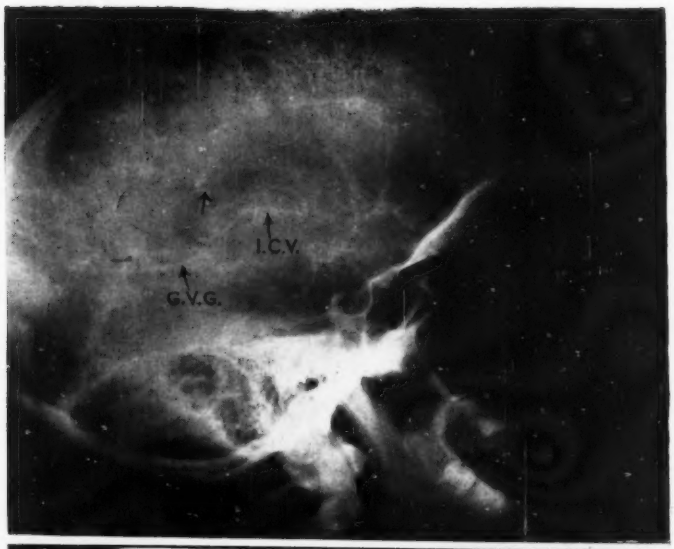


FIG. 25 (at 4·0 secs.).—This corresponds to the usual first phlebogram, taken 2 secs. after the end of the injection. There is now more obvious venous filling of the vessels noted in Fig. 24. There are numerous thin-calibre ascending veins in the frontal region and superficial veins at the Sylvian point. No large veins are seen. Slightly below and in front of the calcified area a small collection of contrast is indicated by an arrow. It indicates the site of filling of the angiomatous malformation.

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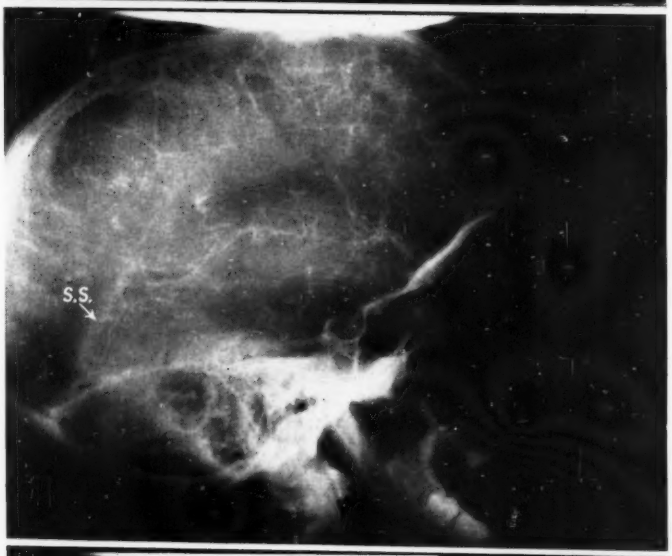

FIG. 26 (at $4\frac{2}{3}$ secs.).—The capillary haze has commenced to clear. There is widespread filling of small veins and the larger veins show more clearly. The straight sinus (S.S.) is clearly seen. The superficial veins are noticeably of much smaller calibre than usual. No anastomotic veins of Trollard or Labbé can be identified.

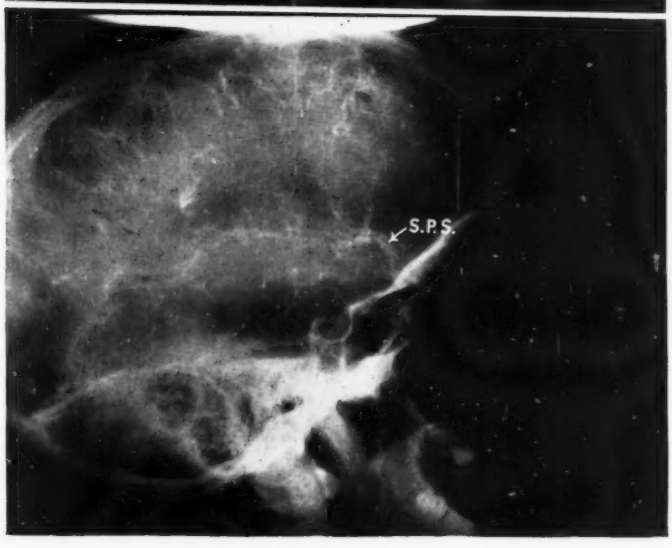

FIG. 27 (at $5\frac{1}{3}$ secs.).—This is a clearer phlebogram. The spheno-parietal sinus (S.P.S.). is seen. The angiomatous collection of contrast previously seen is now more plainly visible and has increased in size.

FIG. 28 (at 6·0 secs.).—This corresponds to the second phlebogram of most clinics, which is taken 4 secs. after the end of the injection. There is marked venous drainage of both the deep and superficial veins. All these vessels appear normal but small in calibre. In the area of calcification no definite abnormality is detected but there is venous drainage by vessels of small calibre. The collection of diodone in front and below it is now quite clearly seen. It measures about 1·0 cm. by 0·5 cm. Passing upward from it there is very faint filling of a large vein (V.) and passing forwards from it are two small veins.

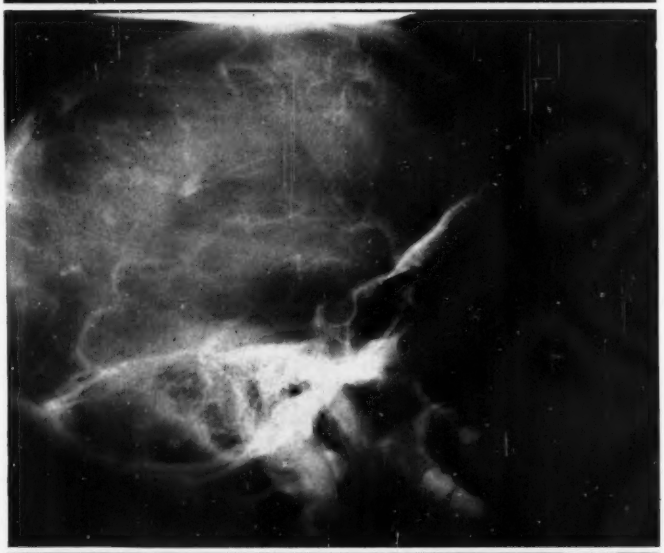

FIG. 29 (at $6\frac{2}{3}$ secs.).—Venous drainage is marked. The angiomatous collection of contrast has increased in size and the veins draining it are better filled. In the calcified area there are some fine vessels faintly filled lying parallel to each other.

FIG. 30 (at $7\frac{1}{3}$ secs.).—The venous drainage of the rest of the hemisphere has commenced to fade. The small veins cannot be seen and the large veins are fainter. By contrast, the angiomatous area is now showing denser filling and more marked venous drainage. The vessels in the calcified area are also better filled.

FIG. 31 (at 8·0 secs.).—The general venous drainage has faded considerably. The venous drainage of the angioma has increased in density and the lesion is now clearly shown.

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FIG. 32 (at $8\frac{2}{3}$ secs.).—There is scarcely perceptible filling of the normal veins but the angioma is most marked.

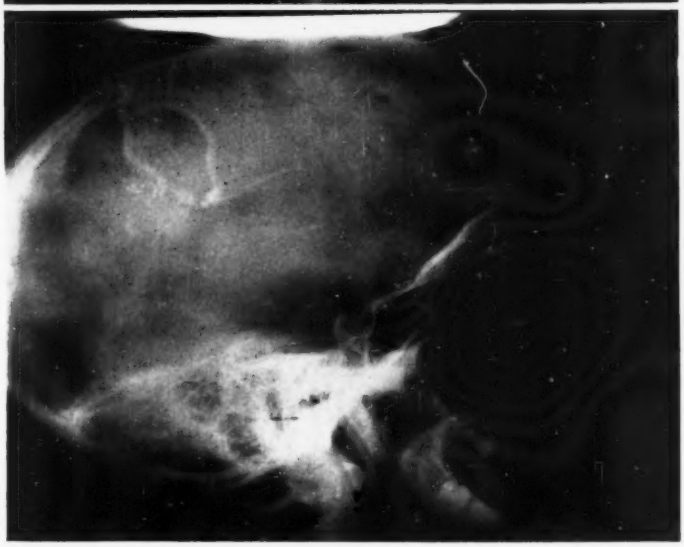

FIG. 33 (at $9\frac{1}{3}$ secs.).—The angioma shows marked drainage. There is still very faint filling of the internal cerebral vein and a posterior vein.

FIG. 34 (at 10·0 secs.).—The angioma still shows marked venous drainage.

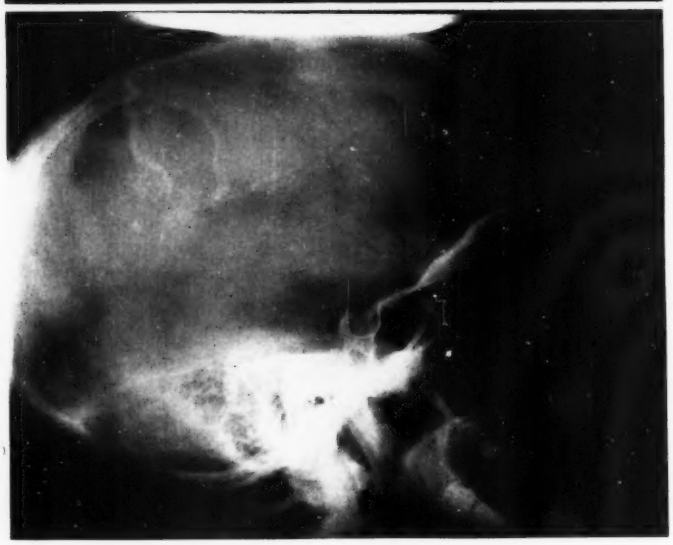

FIG. 35 (at $10\frac{2}{3}$ secs.).—The same. Exposure 18 at $11\frac{1}{3}$ secs. showed the same appearance.

in Case 1. Figs. 19 to 34 reproduce the exposures made in 10 secs. at intervals of $\frac{2}{3}$ sec. These show an angiomatous malformation in the right parietal lobe. It is unusual in showing no abnormal arteries, and in possessing a very slow circulation, a finding which would have been missed in routine angiography.

Discussion

The Normal Angiogram (Case 1).—The normal arterial pattern is well illustrated in Fig. 3, while the appearances during early venous filling are seen in Fig. 7 and the details of later venous filling in Figs. 11 and 12.

The injection of diodone took slightly over 2·0 secs. During the first $\frac{2}{3}$ sec.* the contrast passed down the tubing connexion and up the artery to reach the genu of the anterior cerebral artery (Fig. 2). It has thus travelled about 20 cm. up the artery and a rough estimate of the minimum velocity of the contrast in the artery therefore would be 30 cm./sec.

The first veins showed filling after $2\frac{2}{3}$ secs., and it is of interest to note that they are parts of the deep venous drainage (Fig. 5). Previously it has been held that the deep venous drainage is slower than the superficial: the internal cerebral vein, the great vein of Galen, and the inferior longitudinal sinus are generally shown filled on the phlebogram of the second phase, and not on the first phlebogram (Moniz, 1934; Sanchez-Perez, 1941; Engeset, 1944). In Case 1 the sequence of venous filling is clearly shown to be the opposite of this, for, as

* All times are measured from the first exposure which is taken at the beginning of the injection.

Fig. 5 shows, the deep veins fill first, and the superficial venous drainage appears in later exposures (Figs. 6 to 8), starting in the region of the sylvian point and then spreading upwards. The same order of venous filling was seen in Case 2. There is a rough relation between the time of appearance of diodone in the veins and their distance from the internal carotid artery.

The time taken from the beginning of the injection to the end of the venous drainage was 12·0 secs., the major portion of which was occupied with venous drainage, the time taken for the contrast to traverse the arteries, arterioles, capillaries, and venules being just under 3 secs. After $8\frac{2}{3}$ secs. the deep venous drainage could no longer be seen. The last veins to be seen were the posterior frontal and parietal superficial ascending veins, which had first shown filling at about 4·0 secs. Thus, diodone had been passing through the deep veins for about 6·0 secs. and through the superficial veins for about 8·0 secs.

Overflow.—There are several illustrations of overflow in these two cases. In Case 1 contrast from the left internal carotid could be seen in the left posterior cerebral and the right anterior cerebral arteries (Fig. 3). However, it quickly became fainter (Fig. 4). Overflow occurring at such an early stage ($1\frac{1}{3}$ secs.) may easily be missed in angiography by previous techniques when the arteriographic picture is taken at the end of the injection.

In Case 2 with injection through the right carotid there is also the unusual example of filling of the right and left anterior cerebral, the right middle cerebral, the right and left posterior cerebral arteries (Figs. 20 and 21, taken at $\frac{2}{3}$ sec. and $1\frac{1}{3}$ secs.). In addition, in the same figures, there is seen retrograde filling of the basilar and anterior superior cerebellar arteries. The overflow has faded considerably by Fig. 22 (at 2 secs.), and it would be difficult to detect by the ordinary arteriographic timing.

The Angiomatous Malformation.—In Case 2 the visualization of the angiomatous malformation, seen best at $9\frac{1}{3}$ secs. (Fig. 33), demonstrates the value of this technique in pathological diagnosis. The usual first and second phlebograms, corresponding to Figs. 25 and 28 of this series, would not have given the diagnosis, though the slight unusual collection of contrast seen in these pictures might have aroused suspicion. A second phlebogram 6 secs. after the end of the injection, corresponding to Fig. 31, would have been more informative, but a diagnosis of some form of angiomatous malformation would be all that was possible and the true nature of the lesion would still be obscure. In this case, unlike most angiomas, there are no abnormal arteries and the venous drainage, except from the angioma, is normal. Instead of extremely rapid filling and emptying of the angioma which is seen in other cases, there is here a slow accumulation of contrast in one site followed by an equally slow venous drainage from it. To account for this slow filling of the angioma, the site of the lesion must be distal to the arterioles. There is no evidence of any abnormal arterio-venous communication and this would appear therefore to be a true capillary or small cavernous angioma. This is an unusual type of angioma and, as far as I know, has not been previously demonstrated by angiography, except possibly by Green and Arana (1948). The slow circulation of the malformation was adequately visualized only by the serial films over a long period.

Summary

1. A method of rapid serial angiography has been described which will take twenty-five full-size *x*-ray pictures at intervals of $\frac{1}{2}$, $\frac{2}{3}$, or 1 second.

2. The results obtained by this method in the normal and in a case of angiomatous malformation are demonstrated.

This work would not have been possible without the help of Dr. E. Schuster, O.B.E., who invented and made the apparatus. I wish to thank also Dr. C. de Andrade who assisted in the technique of the percutaneous carotid angiography; Mr. A. F. Nicholls, M.S.R., for the technical skill with which he solved many of the early problems; and Miss D. Haigh, M.S.R., who provided excellent radiographic assistance. Special lengths of *x*-ray film and the photographic reproductions have been supplied by Messrs. Ilford Ltd. The expenses have been met by a research grant from the Nuffield Committee for the Advancement of Medicine, University of Oxford.

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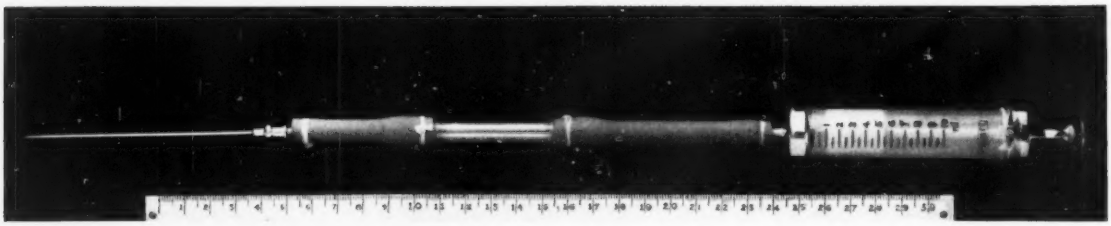

FIG. 1.—The needle and tubing.

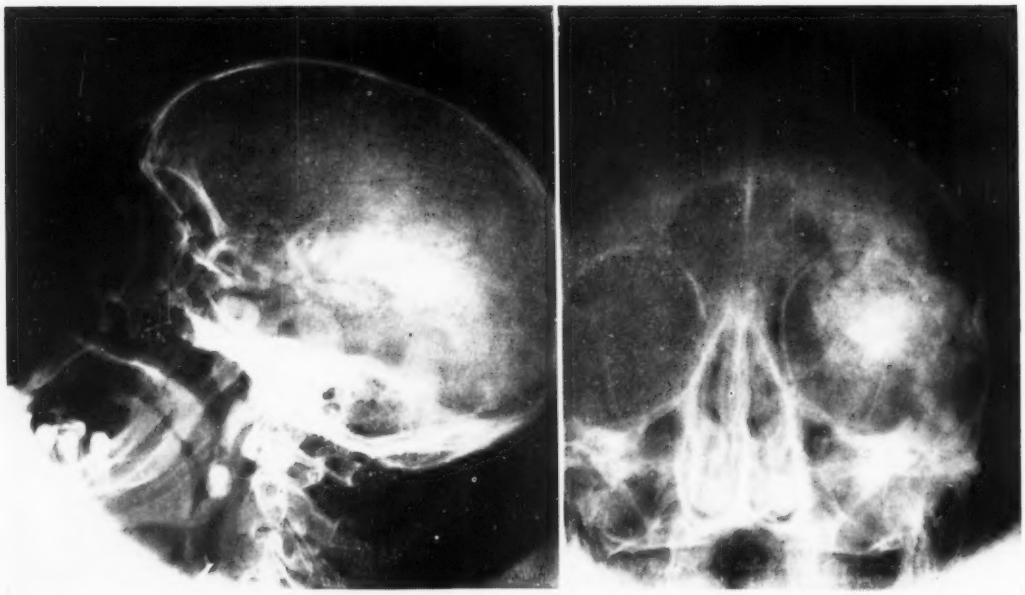

FIG. 2a and b.—Case 1.

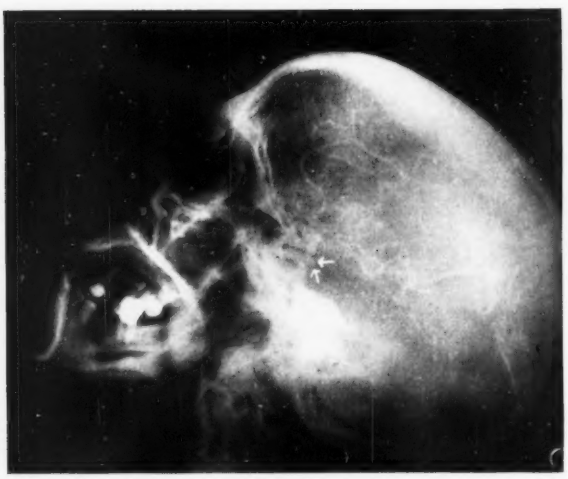

FIG. 3.—Case 2.

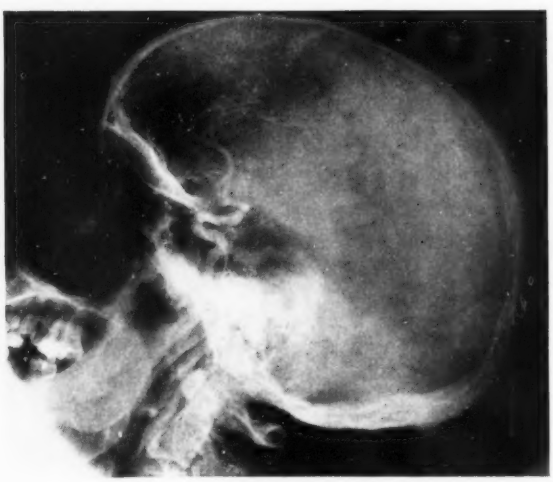

FIG. 4.—Case 3.

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PERCUTANEOUS CAROTID ANGIOGRAPHY

A TEAM TECHNIQUE

WITH A REPORT OF THE RESULTS IN SEVENTY CASES

BY

M. WILKINSON, J. B. STANTON, D. P. JONES, and J. M. K. SPALDING

From the Maida Vale Hospital for Nervous Diseases, London

Percutaneous carotid angiography was used successfully by Egas Moniz (1931), Loman and Myerson (1936), and Shimidzu (1937), but was first perfected as a routine investigation by Engeset (1944) and Lindgren (1947). Lindgren's technique was studied in Stockholm by Bull, who subsequently introduced the method in this country. This paper records the results of a series of cases in which carotid angiography has been performed by a team using a modification of methods described by these writers.

Technique

Anæsthesia and Preparation.—Paraldehyde, 10 ml. intramuscularly, is given as a routine premedication one hour before angiography. For children, rectal avertin in basal anæsthetic dosage is used. Intravenous thiopentone anæsthesia was used for ten patients, but despite its apparent convenience it should be used with caution as it adds the risks of general anæsthesia to the procedure. Green and Arana (1948), however, used general anæsthesia in all their cases.

Apparatus.—A short-bevelled 17-gauge needle 9 cm. long is used for injecting the carotid artery in adults, and a smaller needle is used for children ; these needles are sharpened each time they are used. The needle is attached by a junction to pressure tubing 20 cm. long, in which there is a 4-cm. length of glass tubing (Fig. 1). Standard record junctions are used and are firmly bound to the pressure tubing with linen thread. Other requirements are a hypodermic syringe for local anæsthesia, three 20-ml. Record syringes for saline, and a 10-ml. syringe for the contrast medium which is " Uriodone " in 35 and 50 per cent. solutions. The syringes must fit well and run smoothly, and normal saline solution, heated to body temperature, should be available in ample quantity.

Angiography.—The patient lies supine with his neck extended and his head raised from the Schonander table by a pad and steadied by a head-band. His left shoulder is in close contact with the serial cassette holder. The *x*-ray tube is placed in position for a lateral view of the skull, and a preliminary radiograph is taken. A rubber sheet and sterile towels cover the patient's chest. The first member of the team (the " operator ") standing on the right of the patient, cleans the skin of the neck with spirit, and raising a bleb of local anæsthetic at the intended site of puncture, injects a minimal amount subcutaneously. In most cases the internal carotid artery is punctured at the point where its pulsation is most easily felt. This is usually at the level of the upper border of the thyroid cartilage, where the artery is comparatively superficial in the carotid triangle, lateral to the external carotid artery, and covered by skin, platysma, and deep cervical fascia. If, however, a common carotid angiogram is required, the needle is introduced at the point of maximal pulsation just above the clavicle. The second member of the team (the " assistant ") assembles the needle and tubing and fills them with warm normal saline solution from a 20-ml. syringe. The operator inserts the needle through the bleb of local anæsthetic, and when the needle has penetrated the skin the assistant disconnects the syringe. The operator steadies the artery between the second and third fingers of the left hand and inserts the needle. When the needle is in the lumen of the artery, blood rises at once and can be seen in the glass tubing. The artery is sometimes occluded by the pressure of the needle, and blood only appears in the glass tubing when the needle is slightly withdrawn. When a successful puncture has been made, the assistant again connects the 20-ml. syringe of saline to the tubing and starts to inject at a rate of 15 to 20 ml. per minute. From this time the operator's sole duties are to hold the needle steady in position and to compress the contralateral carotid artery when filling across the Circle of Willis is required.

A lead-rubber screen is pulled down over the neck of the patient to protect the hands of the operator and assistant during exposure, and the *x*-ray machine is switched on. When all is ready, the assistant exchanges the syringe of saline solution for a 10-ml. syringe containing 35 per cent. Uriodone. He injects the whole 10 ml. of contrast solution in three seconds, and when the syringe is still one-third full he calls " shoot " to the radiographer who takes the first exposure (0·75 sec., 70 kV, and 100 ma.). When the exposure is completed, the radiographer calls " pull " to the third member of the team, who removes the exposed film from the serial cassette holder, and calls " shoot " for the second exposure. By a similar routine the second film is

FIG. 1.—The needle and tubing.

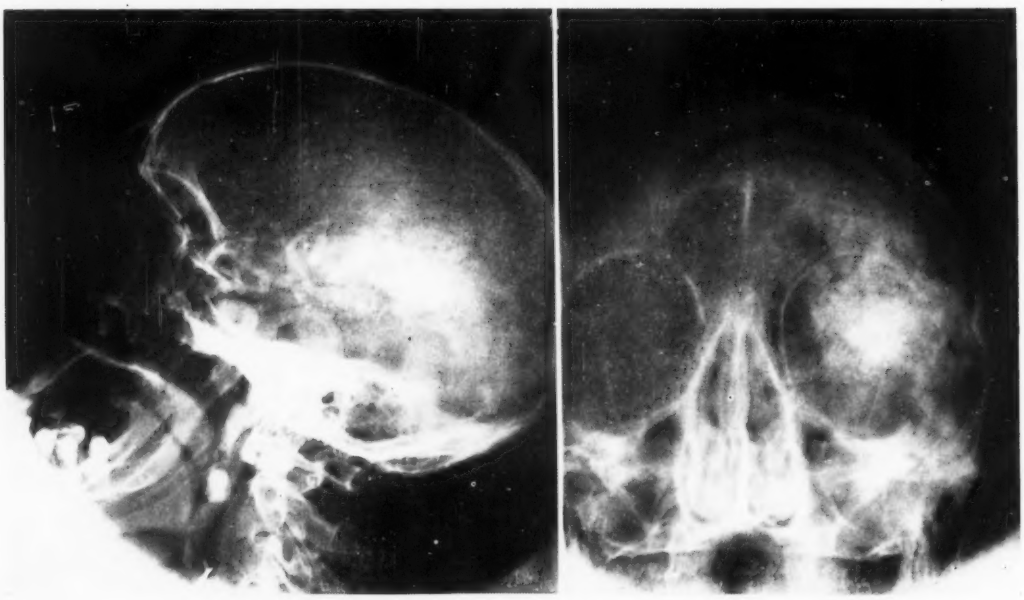

FIG. 2a and b.—Case 1.

FIG. 3.—Case 2.

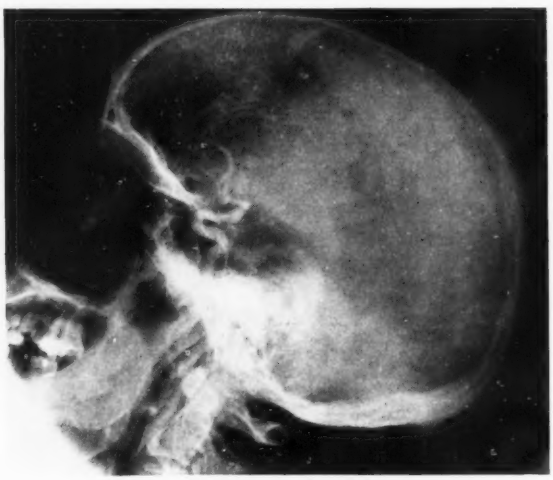

FIG. 4.—Case 3.

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removed and the third exposed. The first picture, taken two seconds after the injection is started, gives an arteriogram, and the further exposures at 3·25 and 4·5 secs. give early and late phlebograms. Between five and six seconds elapse from the beginning of the injection to the end of the third exposure.

The third member of the team inspects the radiographs, which are developed immediately. In the meantime, the assistant perfuses the artery with normal saline while the *x*-ray apparatus is set up for taking an antero-posterior view of the skull. The pad is removed from under the patient's head, and with great care his head is slightly flexed. This is done by the radiographer under the supervision of the third member of the team. Antero-posterior angiograms are then taken, the routine being similar to that for the lateral view with the following exceptions: the contrast solution is 42½ per cent. Uriodone, made by mixing equal volumes of the 35 and 50 per cent. solutions, the exposure is for 1 sec. at 67 kV and 100 ma.; and only two radiographs are taken. A second series of antero-posterior angiograms may be made with compression of the contralateral carotid artery where this is indicated to fill the anterior and middle cerebral vessels on both sides (Engeset and Kristiansen, 1948). Stereoscopic views may be obtained in lateral and antero-posterior planes by taking two series of angiograms with a 6° shift of the *x*-ray tube before the second series.

The third member of the team examines all the radiographs and reports if further angiograms are required. When a satisfactory series of radiographs has been obtained, the needle is removed and firm pressure exerted on the puncture site until all oozing has stopped. Elastoplast is then applied over a piece of dry sterile gauze and is removed after twelve hours.

This technique requires a team of three with the assistance of a radiographer and a nurse. Each of the three members of the team is familiar with every position in the team and takes it in turn to perform the puncture. While angiography can only be performed by a team, it is our experience that a successful puncture will be obtained by one operator soon or not at all, and therefore if the first operator is not successful in a few minutes his place is taken by another member of the team, and if necessary the third member is called upon.

Results

The material consists of seventy angiograms performed on sixty-eight patients whose ages ranged from nine to seventy-two years. Good filling of the cerebral vessels was obtained in sixty-six cases. In fifty cases both lateral and antero-posterior views were good, and in sixteen cases the lateral views were satisfactory but no antero-posterior views were taken. In some cases this was because the diagnosis could be made from the lateral views alone, but in the early cases adequate *x*-ray apparatus was not available for taking good quality antero-posterior angiograms. In thirteen cases it was necessary to make more than one attempt before satisfactory angiograms could be obtained. In only four cases was the examination completely unsuccessful, and in three of these only one attempt could be made. The results of the investigation in the sixty-six successful cases are given in the Table.

TABLE

RESULTS OF SIXTY-SIX ANGIOGRAMS

Clinical diagnosis	Number in which angiography performed	Angiographic appearance	
		Pathological	Normal
Intracranial tumours	16	12	4
Epilepsy	16	1	15
Hæmangioma cerebri	7	7	0
Cerebral arterial disease	5	2	3
Intracranial aneurysm	5	2	3
Diplopia	3	0	3
Other conditions ..	14	2	12
Totals ..	66	26	40

Case Material

Three representative case histories and angiograms are given.

Case 1. Hæmangioma Cerebri.—This man (No. 18586) was aged 36 years. At the age of 12 years, after a minor head injury, he developed right hemiparesis and hemiparæsthesiæ with flashes of light in the right visual half-field. This lasted for a month and since then he has been liable to transient attacks of the same sort, often associated with difficulty in speaking. At the age of 32 he began to have Jacksonian attacks starting in the right hand. Two and a half months before admission he had a probable subarachnoid hæmorrhage. His positive physical signs were a loud systolic bruit in the left parietal region, and some limitation of the right visual half-field. Blood pressure was 150/75 mm. Hg, and the apex beat was displaced one inch laterally (Figs. 2a and 2b).

Case 2. Aneurysm of Internal Carotid Artery.—This was a man (No. 17366) aged 53 years. Five months before admission the vision of the left eye became blurred, and two weeks before admission he developed pain and swelling of the left eyeball and orbit. He was diagnosed as having glaucoma, and the lens was removed. Four days after operation he awoke with a complete right third nerve palsy and occipital headache radiating over the right side of the head to the front. Pain ceased in a week but the palsy persisted (Fig. 3).

Case 3. Thrombosis of Middle Cerebral Artery.—This was a man (No. 19631) aged 44 years. Two years before admission he had three epileptic fits following a " stroke "

which left him with a left hemiparesis. The fits appeared to begin in the left hand. When he was examined he was found to have left hemiparesis with impairment of cortical sensory function over the left side. Blood pressure was 180/100 mm. Hg (Fig. 4).

Complications

The complications described by previous writers include hæmatoma of the neck, thrombosis of the arterial wall at the site of puncture, cerebral embolus, recurrent laryngeal palsy, cervical sympathetic palsy, and iodine sensitivity reactions.

The following were the complications encountered in this series of cases :

Hæmatoma lasting 3 to 7 days ..	2 cases
Cervical sympathetic paralysis lasting 4 weeks	1 case
Urticaria	1 case

Most patients complained of slight soreness at the site of puncture for twenty-four hours after injection, but if digital compression is applied until all oozing has stopped as soon as the needle is withdrawn, there is no danger that a large hæmatoma will form after the patient has returned to the ward. There were a few patients who developed a slight swelling at the site of puncture which did not require special treatment and subsided in two or three days. In all cases in which a second attempt at puncture was necessary, it was found that this could be done within a few days.

One patient, who was known to have had epileptic attacks for several years, had a fit during the investigation ; another patient vomited. In both cases the investigation was continued after a short interval and satisfactory radiographs were obtained without ill effects.

There was one case of cervical sympathetic paralysis which cleared up spontaneously after four weeks.

One patient (Case 1, above) developed slight weakness of his right hand two days after angiography. It was thought that this was caused by progression of his lesion (a large angioma) rather than by the angiography.

On two occasions angiography was performed on patients who were severely ill and stuporose. One patient, who had a large subdural hæmatoma, died five days later. The deterioration in his condition was gradual and did not appear to have been accelerated by the investigation. In the other patient angiography was performed directly after pneumoencephalography when the patient was comatose. This patient had gross generalized cortical atrophy, and died six days later from bronchopneumonia.

Discussion

Using the team technique described above for percutaneous angiography, exposure of the artery at operation was not employed in this series of cases. The complications encountered were also few, and those patients on whom both pneumoencephalography and angiography was performed usually said that the latter was the less unpleasant.

Paraldehyde was used for premedication as it was found that some sedation was desirable. General anæsthesia, in our opinion, is unnecessary in most cases and may even be an added risk.

As a rule the internal carotid artery should be punctured, since better contrast is then obtained with a smaller volume of Uriodone. If, however, there is an indication for filling branches of the external carotid artery, as in a case of suspected meningioma, this should be done by puncture of the common carotid artery low in the neck.

Uriodone has been used as the contrast material in all cases, in concentrations up to 70 per cent., but it has been found that good angiograms can be obtained by using 35 per cent. solution in the lateral view and 42½ per cent. solution in the antero-posterior view. The maximum amount of Uriodone injected in any one patient in this series was 40 ml. of 70 per cent. solution ; there were no ill effects. All patients were tested for sensitivity to Uriodone by instilling two drops of 35 per cent. solution into the conjunctival sac on the day before angiography was to be performed. One patient developed urticaria of the face and neck during angiography, although he had given no reaction to the Uriodone sensitivity test.

Injection of the Uriodone causes a transitory burning sensation in the area of distribution of the vessel punctured. If the common carotid artery has been injected the pain is felt in the teeth, lower jaw, and ear, and if the internal carotid artery is punctured the pain is felt behind the eye. The patient should be warned of these symptoms immediately before injection so that he will not move during the exposures. There is usually flushing of the face and dilatation of the ipsilateral pupil. These symptoms and signs confirm that the contrast material has been satisfactorily distributed through the branches of the artery.

It is most important that neither saline nor Uriodone should be injected unless the needle is in the lumen of the artery. The needle does not become blocked, as a rule, except by clotted blood from puncture of a vein. If it is suspected that this has occurred, the needle should be withdrawn and flushed clear.

Although as a general rule gross hypertension is

regarded as a contraindication to angiography, this investigation was done without ill effect on a patient with a blood pressure of 240/140 mm. Hg.

The complete operation from the injection of local anæsthetic to the removal of the needle usually lasts half an hour, but in one case, in which two sets of lateral and two sets of antero-posterior radiographs were taken, the duration was twenty minutes.

Summary

1. The development of the percutaneous method of carotid angiography is reviewed.

2. A simple technique for a team of three assisted by a nurse and a radiographer is described. Details found to be important are emphasized.

3. The results obtained in seventy angiograms are reported, and three illustrative angiograms with case histories are included.

4. The complications encountered in the series are listed.

We express our gratitude to Dr. W. Russell Brain for his encouragement in the preparation of this report, and to Dr. J. W. D. Bull for his helpful criticism and permission to publish the radiographs.

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EXPERIMENTAL RADIO-NECROSIS OF THE BRAIN IN RABBITS

BY

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Wide acceptance of the statement that the central nervous system is relatively insensitive to *x* rays has undoubtedly encouraged the use of excessive doses for the treatment of lesions in and about this region. A series of human cases has been reported (Pennybacker and Russell, 1948) in which massive focal necrosis and gliosis of the brain followed at some period after therapeutic irradiation. The latent period varied from nine months to five years. In two of these (Cases 1 and 2) the changes occurred in areas that were presumed, on reasonable grounds, to have been previously normal ; in the remainder the picture was complicated by a pre-existing or co-existing tumour. Nevertheless the general pattern of the tissue alterations was consistent throughout the series, and agreed with descriptions already published by others.

We concluded, from the histological appearances in the human material, that the degeneration, necrosis, and hæmorrhage were brought about by profound circulatory disturbances resulting from the vascular changes also demonstrated. These included fibrinoid necrosis of the walls, thrombosis, and pronounced collagenous thickening of the perforating vessels. The wide-spread distribution of extra-vascular fibrin filaments throughout the affected areas of the cerebrum, and independent of hæmorrhage, pointed to an increased permeability of the vessels as a part of the process. And in Case 1 the presence of granules of thorotrast in and outside the walls of vessels in the affected area provided additional evidence of this.

But any estimate of the precise sequence of events in such a fully developed lesion must be largely guesswork unless this can be studied experimentally Hence an attempt has been made, in the work to be described, not only to reproduce the lesions seen in the human subject but also to study their evolution and, in particular, the part played by structural alterations in the blood vessels. These experiments were briefly mentioned, in an incomplete stage of the work, in an earlier communication (Russell, 1946).

Experimental

Monkeys and dogs not being available for our purposes we used rabbits. Our first experiments, using a single trial surface dose of 2,850 r, proved successful in the induction of lesions, accompanied by neurological disturbances, after a latent period of about a hundred days. We then examined the brains of similarly treated animals at different periods before the time at which symptoms were anticipated in order to demonstrate earlier stages. In other experiments we reduced the *x*-ray dosage to find the level at which histological changes would fail to appear, and to examine the relation between the dose given and the latent period.

Technique.—Unanæsthetized young adult rabbits of no special breed received a single dose of *x* rays directed to the left side of the skull, the scalp being unshaved. The radiation was generated at 200K (Villard Circuit) filtered by 0·5 mm. Cu. and 1·0 mm. Al to give a half-value layer of 0·95 mm. Cu. Field size 3×4 cm. ; surface dose-rate 154·5 r per minute. Focus—skin distance 25·5 cm. With the conditions the approximate depth doses are : 1 cm. depth, 85 per cent. ; 2 cm. depth, 70 per cent. ; 3 cm. depth, 57 per cent. Group I (13 animals) received 2,850 r ; Group II (5 animals) 2,440 r ; Group III (2 animals) 2,030 r ; Group IV (2 animals) 1,625 r. The dose stated is that at the surface in each case, delivered as one exposure.

Under these conditions a rectangular patch of epilation appeared in the scalp, in animals surviving one month or longer, which was bounded medially by a sagittal line corresponding either to the centre of the skull or a few mm. to the right of it ; anteriorly it generally fell just behind the palpebral fissure ; laterally it overlapped the temporal muscles and passed backwards to skirt the base of the left ear and usually extended over the back of the skull covering the left side of the cerebellum. In animals of Groups I and II the skin at late stages lost its suppleness and became dry and scaly. In those of Group I which survived longest the centre of the affected skin sometimes became ulcerated and scabbed.

The animals were killed by bleeding them from the carotid arteries when deeply anæsthetized with chloroform. The brain was then removed, fixed in 10 per cent. formaldehyde, and divided coronally, when hardened, with slices about 2 mm. thick. The cerebellum was obliquely divided on each side so that the paraflocculus remained attached (Fig. 1). Most of the blocks were embedded in paraffin wax, but some were cut on the freezing microtome and stained by various silver techniques, and for fat. Paraffin sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, Weigert's fuchselin for elastic fibres and neutral red, and phosphotungstic-acid hæmatoxylin.

Group I

2850 r: Thirteen Animals

Apart from one rabbit, which died of intercurrent disease on the twenty-first day after irradiation, all remained in normal health until sacrificed or, if allowed to survive, until about the hundredth day. On the ninety-ninth, hundred and third, and hundred and fourth days respectively three of the animals became irritable, lost interest in their food, and developed neurological signs including transitory attacks of head-retraction accompanied by salivation, circling movements which were usually towards the right, and phases of nystagmus. Two of these animals were killed, at forty-eight hours and fourteen days respectively, after the development of symptoms; the third was allowed to survive for a further six weeks. By this time it appeared blind and unable to feed itself and was therefore killed. These three rabbits, which will be referred to as "post-symptomatic" examples, all showed extensive irradiation lesions of the brain.

The remaining nine animals of the series were killed before the development of symptoms at seven, twenty-six, fifty-seven, seventy-three, seventy-six, eighty-two, eighty-five (two animals), and ninety days after irradiation, with the object of demonstrating earlier lesions. The search was successful in three; at eighty-two, eight-five (one animal) and ninety days. These will be referred to as "pre-symptomatic" examples. The remainder showed no histological changes in the brain. With the object of demonstrating possible changes in capillary permeability five of the rabbits were given an intraperitoneal injection of trypan blue (20 ml. of a 1 per cent. solution per kg. of body weight) twenty-four hours before death. These were killed at seven, twenty-six, fifty-seven, eighty-five, and one hundred and forty-three days after irradiation.

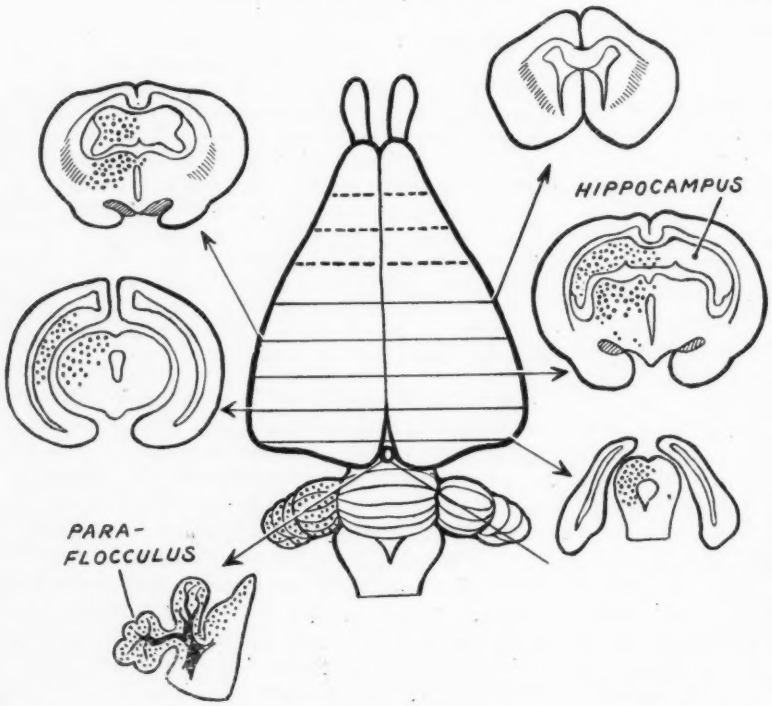


FIG. 1.—Diagram of rabbit's brain. Straight lines represent planes of section; arrows directed to show pattern of structures on corresponding cut surfaces. Dotted areas on latter represent sites of observed lesions.

Pathological Changes in Group I

Macroscopic. — Alterations in the skin of the irradiated area have already been noted. In none of the rabbits examined before eighty-two days were any further changes found. After this period dissection revealed fibrosis of the subcutaneous tissues; the scalp and temporal muscles were often abnormally adherent to the skull. The skull itself showed no change beyond pallor in the irradiated area when viewed by transmitted light. The meninges were invariably unaltered. The brain, too, showed as a rule no superficial changes beyond diffuse orange or café-au-lait pigmentation of the left side of the cerebellum (three animals; Fig. 2) accompanied, in one, by a few petechial hæmorrhages in the same areas. Occasionally the hind-end of the left cerebrum

appeared slightly fuller than on the right.

On section no alterations were found before the eighty-second day after irradiation. In the rabbit killed at this stage a limited area, about 4 mm. in diameter, of the left lobe of the cerebellum showed slight diffuse yellowish discoloration of the cortex, with a few punctate hæmorrhages. The paraflocculus was not affected. At eighty-five days (two rabbits) and ninety days no changes were visible to the naked eye. In the *post-symptomatic examples* there were ill-defined grey or yellowish-grey patches of discoloration in deep-seated parts of the hind end of the left cerebrum, the left basal ganglia, and left dorsal quadrant of the mid-brain (Fig. 1). The cerebral areas affected were the dorsal part of the left hippocampus, the left fimbria, and the adjacent parts of the basal ganglia. The folia of the left lobe of the cerebellum were shrunken and yellowish in those animals which showed superficial discoloration ; in one of these the paraflocculus was similarly involved, and in another there were a few petechiæ in the adjacent left side of the medulla oblongata. It is particularly noteworthy that the cerebral cortex in the irradiated area was unaltered except in the animal, killed at 143 days, which received trypan blue. This, the most advanced of the series, showed a diffuse patch of blue coloration over the lateral border of the hemisphere and similar staining of the necrotic foci in the deeper tissues.

Microscopic Examination.—No changes were identified in rabbits killed before the eighty-second day after irradiation. Early changes were found in the pre-symptomatic group and progressively later stages in the three post-symptomatic examples. No changes, however, were found in one of the two animals killed at eighty-five days.

The *earliest lesions* found, at eighty-two, eighty-five, and ninety days, consisted of minute ball- and ring-hæmorrhages, too small to be seen with the naked eye, which lay in the dorsal part of the left hippocampus, the adjacent lateral border of the basal ganglia, and the left dorso-lateral quadrant of the mid-brain (Fig. 1). The same areas, in the rabbit at eighty-two days, contained a few foci of anæmic necrosis of similar size. Both the hæmorrhagic and anæmic foci were generally near a capillary but sometimes surrounded an arteriole. The basement-membranes of these capillaries appeared rather blurred and stained feebly with the usual aniline dyes ; the endothelial cells were often swollen but were free from any demonstrable nuclear degeneration or fatty change ; the lumina contained discrete red corpuscles. Occasionally spheroidal particles, from about 4 to 8 μ, staining like fibrin with phosphotungstic-acid hæmatoxylin, appeared in the tissues near the walls of these vessels. In silver preparations amœboid forms of microglia had collected in these perivascular foci and some cells had ingested red corpuscles, but as yet contained no Sudanophil droplets. There was no gliosis. Bielschowsky preparations showed well-preserved neurones in all areas, and even in the neighbourhood of the perivascular lesions. Axis-cylinders were fragmented in the centre of some foci, but in places traversed them intact.

Changes were present in the cerebellum in two of these animals, but appeared more recent in the rabbit killed at ninety days than at eighty-two days. In the former, a few cortical hæmorrhages occupied the layer of Purkinje cells and there was considerable focal degeneration of these cells. No vascular changes were observed. At eighty-two days, however, there were many more hæmorrhages, affecting all the cortical layers, distorting their pattern and accompanied by a good deal of œdema. There was a patchy loss of the Purkinje cells, especially at the summits of the folia, and associated here with gliosis resulting from multiplication of the Bergmann cells (Fig. 3). The perforating blood vessels were rather tortuous and, in silver preparations, showed collagenous thickening. Foci of microglial reaction were present in all layers, including the sub-cortical white matter, the appearances being similar to those already described in the cerebrum. In Bielschowsky preparations no notable changes were found ; the axis-cylinders were often tortuous but were intact except in areas of tissue destruction. A few " torpedoes " were however found attached to Purkinje cells.

The three *post-symptomatic examples* showed progression of the damage both in respect of the actual size of the areas involved and also in the presence of old as well as recent lesions. While the distribution of the lesions retained the same character as in those already described (Fig. 1) there appeared a tendency for the necroses and hæmorrhages to spread both ventrally and towards the right cerebrum, but in the cerebellum they did not cross the mid-line. In these cerebral extensions homologous structures were usually involved. Thus in the rabbit that survived to 143 days there were recent hæmorrhages and necroses even at the frontal poles, occupying the central white and adjacent grey matter ; the left pole was more affected than the right. Patches of necrosis also appeared in the optic tracts on either side of the tuber, thus accounting for the blindness (Fig. 4). Here again the left side was more affected than the right. In this animal the cerebellum escaped damage ; correspondingly it was noted that the area of epilation was more anterior than usual, its

anterior border being at the level of the palpebral fissure. In the animal killed at 118 days the cerebellar cortex of the left lobe showed advanced gliosis (Fig. 5), with destruction of many neurones and considerable collagenous thickening of the perforating blood vessels (Fig. 6). But progression of the lesion in the cerebellum here was also demonstrated by fresh hæmorrhages and necroses (Fig. 7).

The oldest lesions in the cerebrum of these three rabbits were confined to the sites where they were first identified in the pre-symptomatic group (Fig. 8). In and about these there was dense gliosis, the astrocytes being exceptionally large, with bulky cytoplasm and stout fibrillated processes (Figs. 9, 10). Iron-pigment within microglial cells indicated the sites of earlier hæmorrhages. Many fat-granule cells were found in the borders of the necrotic areas. Fresh necroses and hæmorrhages were, however, mixed with the older lesions in all areas where the latter were found (Fig. 11). In these three animals further pathological developments were found in the perforating vessels associated with the lesions already described. Thus in occasional arterioles and capillaries the walls had undergone fibrinoid necrosis (Figs. 12, 13), and some of these were occluded by thrombus. In the longest surviving rabbit a group of vessels in the left hippocampal gyrus showed great dilatation with thickening of the walls by œdema, fibrin, and reduplication of collagen fibres (Fig. 14). In this animal alone were a few hæmorrhages found in the subcortical white matter of the posterior third of the left cerebrum. In the area of cortex that was vitally stained with trypan blue there was an amœboid change in the microglial cells, but no further histological alterations were demonstrated. It is remarkable that, in the group as a whole, the cerebral cortex and meninges remained unchanged.

Group II

Five rabbits each received 2,440 r, the physical conditions being the same as before. Two developed intercurrent disease and were killed, at eighty-nine and 194 days respectively, after irradiation. They showed no cerebral changes due to the experiment. Two others spontaneously developed neurological symptoms of the kind observed in Group I at 239 and 240 days respectively, and were then killed. The fifth had several episodes of irritability, with indifference to food, at about 240 days ; after this it recovered and appeared normal. It seemed well when killed at 355 days. These three rabbits all showed advanced changes, similar in distribution and character to those noted in the post-symptomatic members of Group I. In one animal, however (239 days), the cortex of the left cerebral convexity, at the coronal level of the tuber cinereum, showed recent hæmorrhages in the deeper laminæ. The cortex as a whole appeared slightly atrophied in this region. It is perhaps significant that this rabbit became suddenly ill, with irritability and retraction of the head upwards and to the left, and it flopped repeatedly on to its left side. There was a rapid flickering of the right eye, the left eye being almost closed and immobile. There was rapid, panting respiration and excessive salivation. This rabbit was killed two hours after the development of symptoms.

In comparison with Group I the vascular changes were more pronounced ; not only was fibrinoid necrosis more conspicuous but there was, in addition, a good deal of hyaline collagenous thickening in occasional foci. It is noteworthy that, in all three animals, fresh hæmorrhages and anæmic necroses were conspicuous in addition to older lesions.

Group III

Two rabbits each received 2,030 r by the same technique. They were kept for fifteen and twenty-five months respectively and remained normal. Their brains showed no abnormality.

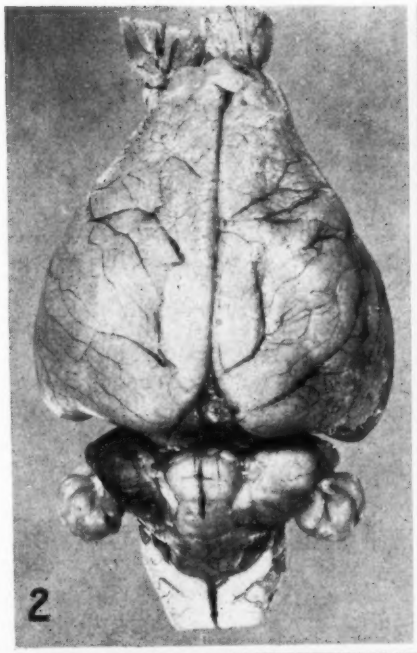
Group IV

Two rabbits each received 1,625 r and were kept for fifteen and twenty-four months respectively. They also remained healthy and their brains were normal on microscopical examination.

Discussion

Comparison of the histological effects produced in these rabbits with those recorded in human material (see literature in Pennybacker and Russell, 1948) shows a close correspondence in the range and character of the delayed lesions that arise in the brain after *x* irradiation. It is important to emphasize the existence of this latent period, during which the subject may enjoy normal health and vigour, because certain more diffuse, mainly neuronal, changes have been described as the *immediate* effect of *x* irradiation in experimental animals. We are not concerned with these here.

Delayed necroses of the brain, associated with degenerative and obliterative changes in the blood vessels, have been produced by *x* rays in the dog by Lyman and others (1933). Of the four dogs used, one survived for six months and showed lesions of this kind ; in the other three, which were killed at seven days, five weeks, and six weeks, there was no obvious change in the first and " acute meningo-encephalitis " was described in the other two. Davidoff and others (1938) produced a variety of local effects in the brain in a series of



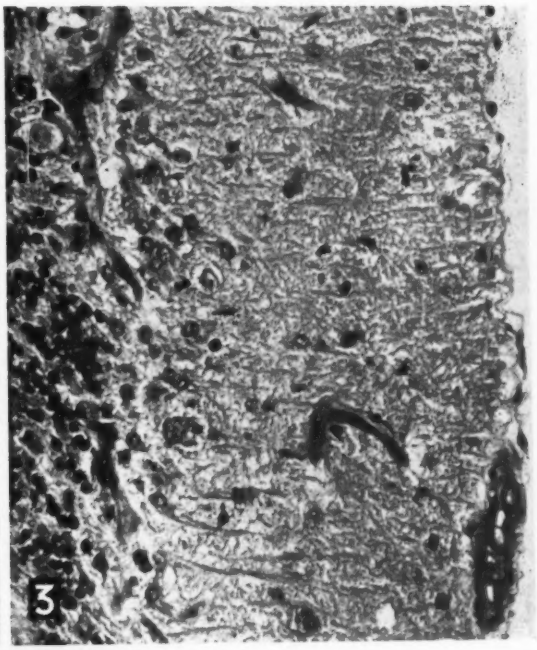


FIG. 2.—Group I; 101 days. Brain showing pigmentation of left lobe of cerebellum.

FIG. 3.—Group I; eighty-two days. Cerebellar cortex showing loss of Purkinje cells and early multiplication of Bergmann cells. Hæmatoxylin and eosin, ×240.

FIG. 4.—Group I; 143 days. Arrows indicate pale areas of necrosis in optic tracts. Phosphotungstic-acid hæmatoxylin, ×12.

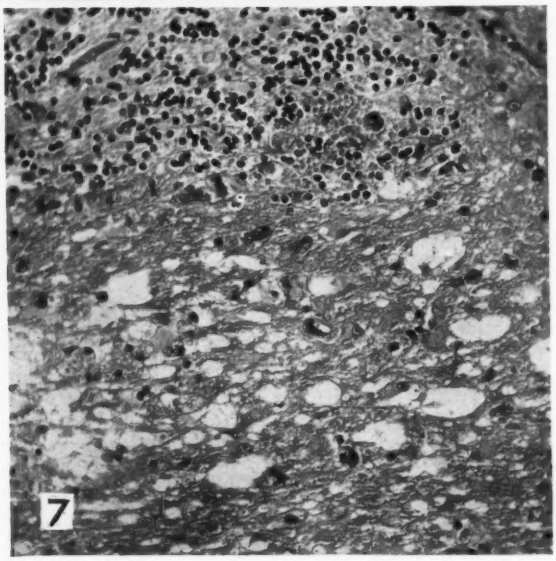


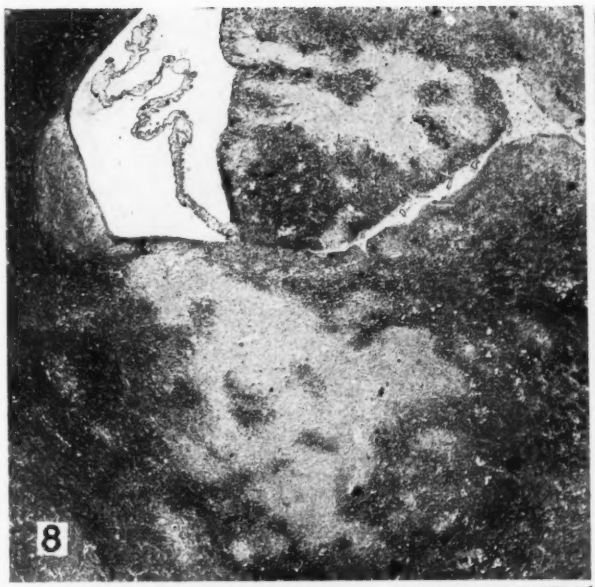
FIG. 5.—Group I; 118 days. Cerebellar cortex to show radial gliosis. Silver carbonate, ×190.

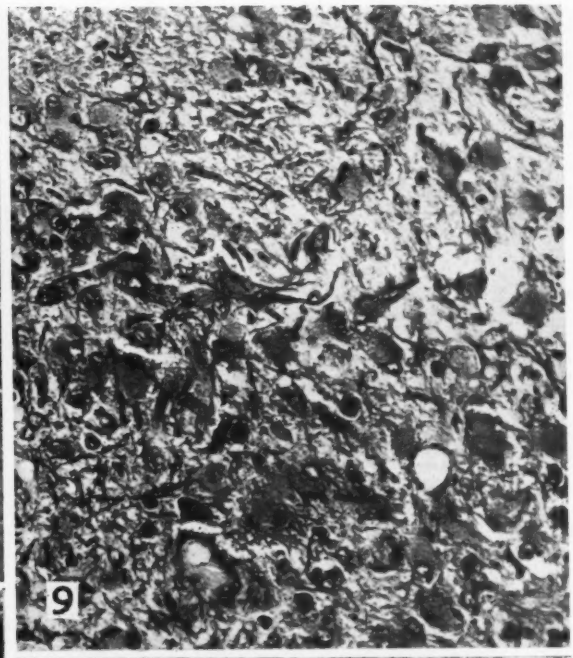
FIG. 6.—As in Fig. 5. Destruction of cortical pattern and collagenous thickening of blood vessels in another area. Silver carbonate for reticulin, ×160.

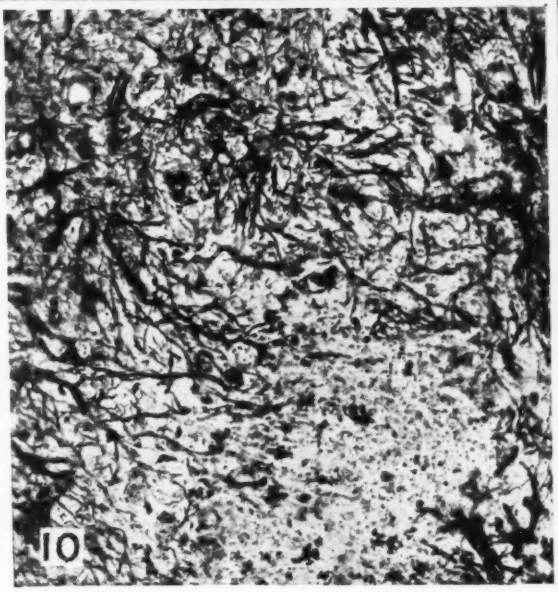
FIG. 7.—As in Figs. 5 and 6. Deeper area showing a fresh hæmorrhage in border of granule-cell layer and vacuolar necrosis in adjacent white matter. Hæmatoxylin and eosin, ×160.

rhesus monkeys. They varied their single dose of *x* rays from 5,000 to 1,000 r and obtained, with doses of from 2,000 to 3,000 r, a hemiparesis that developed after several months due to softening in the irradiated hemisphere. Although they observed occasional hyaline changes and collagenous thickening of related blood vessels, they inclined to the view that the primary effect of the *x* rays was upon the parenchyma of the nervous system.

From our own observations, both on human material and in these rabbits, it appears that vascular damage plays an important, if not determining, part in the production of the lesions though it may not be responsible for the complete histological picture. Thus the earliest change recognized, in rabbits killed shortly before neurological symptoms were anticipated, consisted of minute perivascular hæmorrhages and anæmic necroses. Gliosis quickly







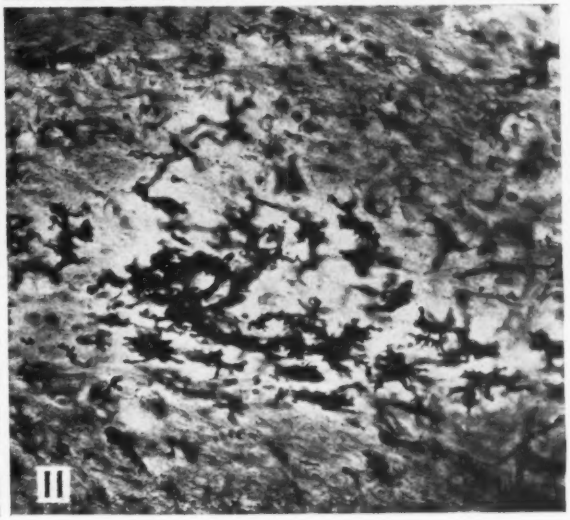


FIG. 8.—Group I ; 143 days. Pale areas of necrosis in left basal ganglia and fimbria (above). Phospho-tungstic-acid hæmatoxylin, × 15.

FIG. 9.—As in Fig. 8, to show gliosis at border of necrotic area, × 270.

FIG. 10.—As in Fig. 9, to show glial fibres. Weil-Davenport, × 190.

FIG. 11.—As in Fig. 10, showing adjacent early necrosis with active microglial reaction, × 230.

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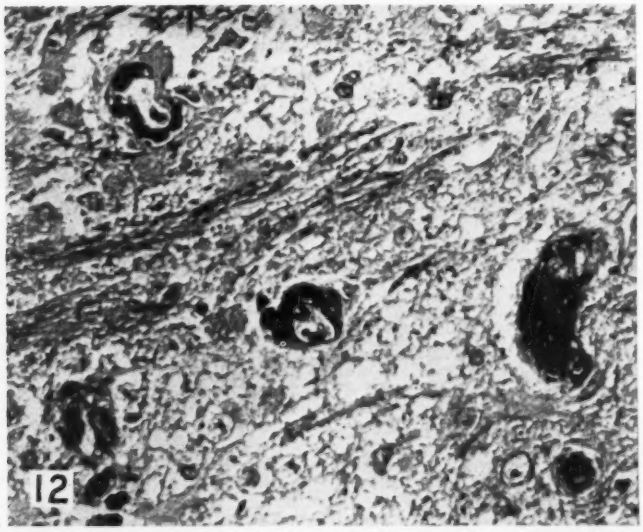
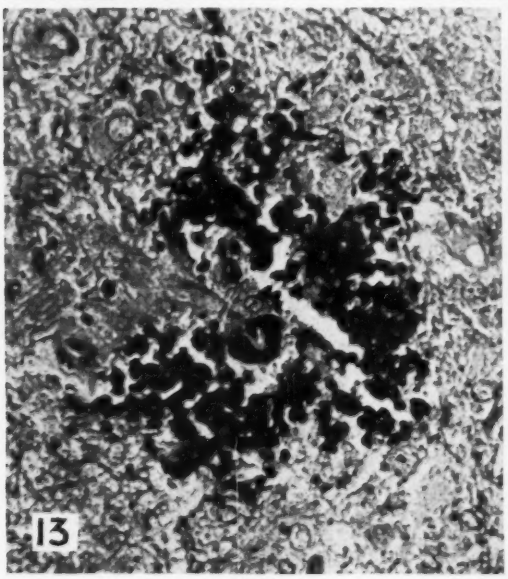
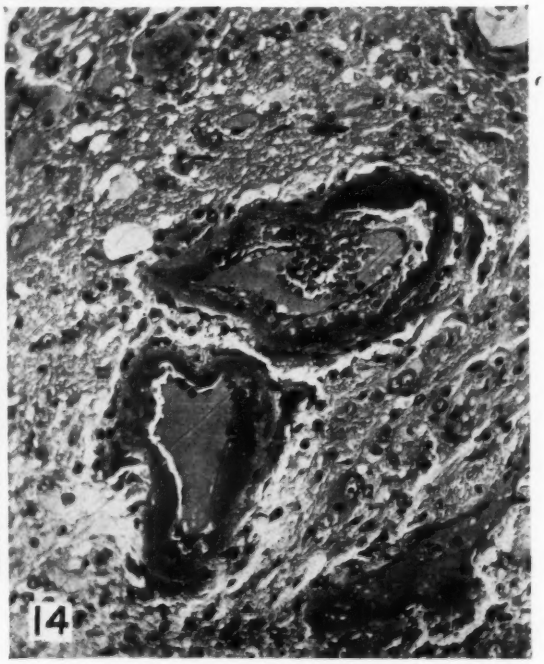


FIG. 12.—Group I ; 101 days. Vessels in left basal ganglia showing fibrinoid necrosis of walls and (right) thrombosis. Phosphotungstic-acid hæmatoxylin, ×360.

FIG. 13.—Group I ; 118 days. Recent hæmorrhage in mid-brain about vessel showing fibrinoid necrosis. Phosphotungstic-acid hæmatoxylin, ×400.

FIG. 14.—Group I : 143 days. Vessels in left hippocampus showing expansion of walls by fibrinoid material, œdema and collagenous thickening. Hæmatoxylin and eosin, ×190.





followed. At the earliest stage no alteration could be demonstrated in the walls of these vessels beyond swelling of the endothelial cells and poor definition of the basement membranes of the capillaries. In rabbits killed two or three weeks later the vessels occasionally showed a frank fibrinoid necrosis sometimes accompanied by thrombosis (Figs. 12, 13). Collagenous thickening was demonstrated in addition (Fig. 14).

Irradiation necrosis, when once initiated, appears to progress with remarkable rapidity. In our animals it began in the irradiated area and later extended more widely beyond the immediate field. This was demonstrated in the rabbit that survived six weeks after the onset of symptoms. The distribution of the initial lesions was remarkably constant and, at first sight, curious in that the deeper parts of the left cerebrum were affected whereas in the cerebellum the cortex appeared to bear the main brunt. Possibly the greater thickness

of the skull over the hind-brain may have been a factor in this, although even an additional thickness of 2 mm. would not have absorbed more than 8 per cent. of the radiation. The immunity of the meninges and of the cerebral cortex was remarkable. In only two rabbits were lesions demonstrated in the cortex, and they were confined to the deeper strata.

Though the number of animals irradiated was small there was a definite indication, comparing Groups I and II, that reduction of the dose of *x* rays (from 2,850 r to 2,440 r) more than doubled the latent period. For this reason it was considered advisable to maintain the animals of Groups III and IV for a proportionately longer period (up to two years). From the absence of any demonstrable lesions in the latter groups it seems likely that the minimal single surface dose of *x* radiation of the quality used that will evoke delayed radio-necrosis in the rabbit's brain lies somewhere between 2,440 and 2,030 r.

The pathogenesis of this delayed radio-necrosis is difficult to conceive. Close microscopic examination of the tissues during the latent period has yielded no clue. And when the earliest foci of hæmorrhage and necrosis are detected it is difficult to interpret their pathogenesis in the absence of any fatty or fibrinoid changes in the walls of the associated blood vessels. Fibrinoid necrosis soon appears, but it has not, in these animals, preceded the parenchymal changes. It may, however, be supposed that some alteration in the permeability of the vessel walls, unaccompanied at first by any obvious structural changes, initiates the pathological processes. The presence of small spheroidal particles, with the staining qualities of fibrin, that are found about some of the vessels in the earliest stages would support this hypothesis. Scholz and Hsü state that there was some indication, in two of their schizophrenic patients, that an increase of permeability took place at the end of four and a half to six and a half weeks respectively after irradiation. But they do not give the evidence for this statement. The widespread distribution of fibrin and the presence of extravascular granules of thorotrast (Case 1) in our human examples (Pennybacker and Russell) indicate an increased permeability when the lesions are advanced. Similarly a local increase of permeability was demonstrated in the most advanced of our series in Group I, when trypan blue was injected before death (see above p.189). But a similar test performed in the pre-symptomatic stage yielded negative results at seven, twenty-seven, fifty-seven, and eighty-five days. It is of interest that, in the last of these, early lesions were identified with the microscope. There is therefore no evidence from our experiments that an increase in vascular permeability precedes the development of parenchymal lesions.

It cannot of course be assumed that the evocative dose of *x* rays for the rabbit's brain will be followed by similar changes in other species. One of us (K.T.) subjected a series of mice to the dose received by the rabbits of Group I: neither histological effects nor neurological symptoms were noted in survivors up to twenty weeks.

Conclusions

A single *x*-ray dose of 2,850 r, under the physical conditions that have been defined, will produce delayed irradiation-necrosis in the rabbit's brain after a latent period of approximately one hundred days.

The latent period is lengthened by reducing the dose to 2,440 r.

The initial histological changes consist of minute foci of hæmorrhage and necrosis which are intimately related to the perforating vessels and, in particular, capillaries. Increase of capillary permeability accompanied the established lesion but was not demonstrated at earlier stages.

The lesions, when once initiated, appear to extend rapidly, and to progress to non-irradiated parts of the brain. They are characterized, in later stages, by pronounced gliosis, and by progressive degeneration and sclerosis of the adjacent vessels.

The neurones are only focally and secondarily affected.

The meninges and their blood vessels are unaffected, and the superficial parts of the cerebrum escape, although the cerebellar cortex may be extensively damaged.

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AFTER-IMAGERY IN DEFECTIVE FIELDS OF VISION*

BY

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In a study of visual after-images of patients with homonymous hemianopia one would anticipate an after-image only in that part of the field which is perceived by the patient during fixation. Fuchs (1920, 1921), however, found that such patients saw more in the after-image than in the stimulus field or the perceived field of vision. Thus Fuchs noted that a figure only partly seen on fixation (the remainder of the figure was not seen because it was situated in the blind part of the field) was perceived by the same patient in its entirety in the after-image. This is known as the phenomenon of completion.† Using simple figures, such as circles and squares, Fuchs postulated that completion depended on the "inner structural requirements of the stimulus figures." On the other hand, Bender and Teuber (1946), who also studied completion effects in impaired fields of vision, and used complex figures such as an American flag in complementary colours, believed that these effects need not necessarily be explained only by qualities of the stimulus figure. They observed that the after-image may represent only partial tendencies toward completion. Thus additional areas seen in the after-image or the "completed areas" did not always produce a smoothing of contours or the completion of a total figure. Sometimes there occurred in the after-image irregular additions to that which was perceived in the stimulus field.

The present investigation was undertaken to study the nature of after-image alterations in a patient with irregular but homonymous defects in the fields of vision following lesions in both occipital lobes. The test patterns used were simple geometric figures.

Case Report

J. G., a forty-year-old salesman, was admitted to the Mount Sinai Hospital in the latter part of 1946 because of occipital headaches, generalized weakness, and "bizarre" visual disturbances. There was a long-standing history of hypertension and arteriosclerotic cardiovascular disease. His average blood pressure during the illness was 200/120 mm. Hg. A bilateral sympathectomy for relief of hypertension had been performed in 1945. During the course of his long illness he had symptoms and signs of embolization to the lungs, kidneys, popliteal artery, and brain.

The cerebral infarcts which first occurred in 1942 were clinically localized to the occipital lobes. The visual symptoms consisted of episodes of blurring of vision to the left of his fixation point, spells of momentary blindness, teleopsia, micropsia, monocular diplopia, and dysmorphopsia. The perimetric and tangent screen examinations of the visual fields showed homonymous scotomas in the left upper quadrants and macular regions. There was also a relative scotoma in a small region of the right field of vision as indicated in Fig. 1. In 1946, and on admission to the Bellevue Psychiatric Hospital in 1948, a marked dissociated nystagmus was noted whenever he tried to view an object in his left field of vision. In the spring of 1948, the patient became worse, and he died in cardiac failure. Autopsy examination was limited to the brain. This revealed areas of infarction on the under surface of both occipital lobes. The ischæmic softening was greatest on the right side and extended forward but not into the temporal lobe. It included Brodmann's area 18, the inferior calcarine region of area 17, and the tip of the occipital pole. The lesion on the left was limited to a small region in Brodmann's area 18.

Method of Testing Visual After-Imagery

The figures (stimulus fields) used to elicit visual after-images consisted of various sized red and green coloured squares presented to the patient on a white background. Six different patterns were presented (series 1 to 6, as illustrated in Figs. 2 to 7). Binocular fixation was maintained on a small cross in the centre of the stimulus field. After sixty seconds' fixation the stimulus field was manually removed and the patient continued to fixate on a small cross on the white background which now served as the post-exposure or "after-field." Immediately, or a few seconds thereafter, the patient reported that he saw an after-image which was always a negative after-image. Conditions of illumination were varied. Usually the patient was seated at a desk and the stimulus and back-

* This work was aided by a grant from the Dazian Foundation of Medical Research, New York.

† The term "completion" as used in this paper will signify any extension of area of the perceived field in the after-image field.

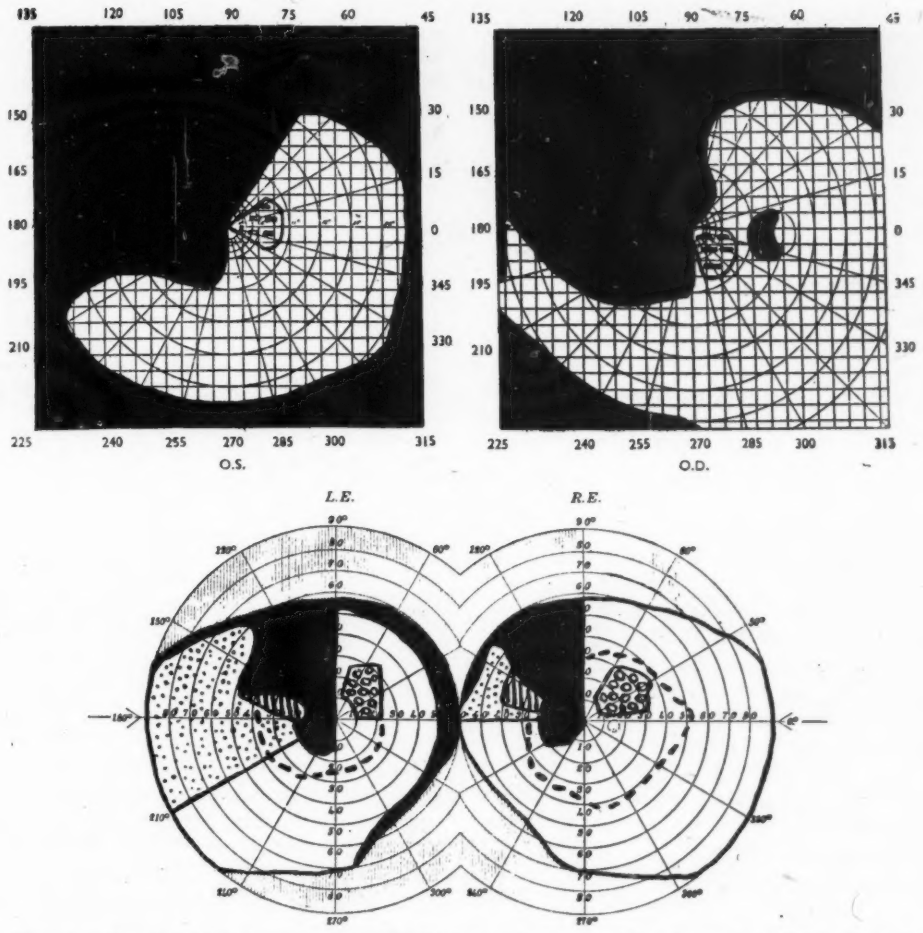

FIG. 1.—Visual fields (*a*) perimetric and (*b*) tangent screen. Illumination daylight, size of target 5 mm., distance 33 cm. Solid black indicates region in which perception of movement is absent. Vertical lines indicate area in which movement is perceived but there is marked blurring and fluctuation in the appearance of the target. Stippling represents area in which target is less blurred. The small circles within the right field indicate region in which vision was blurred or grey. The dashes represent the borders of the field of vision for colour red.

ground were exposed to ordinary desk lamp illumination. When the patient was confined to bed, only daylight illumination was employed. There was no appreciable difference between the results obtained under either type of illumination. The patient's eyes were approximately 30 cm. from the fixation point, and no more than seven or eight tests were made at any one session.

Results

Stimulus Field.—On fixing at the centre of the stimulus field the contour of the pattern actually seen by the patient corresponded to his field as plotted on the tangent screen (Fig. 1b). Under such conditions the area to the left of the fixation point was generally not reported. The line of division in the vertical meridian was irregular. It was somewhat S-shaped, as noted on the perimetric and tangent screen recordings. The lower left quadrant of the stimulus pattern was perceived only when large patterns were exposed, but colour was not well seen in this quadrant. To the right of the fixation point there was also an area of defective vision. This area varied in size and shape, and was reported by the patient as appearing " grey with white spots." (Figs. 1 to 7.) In the right superior quadrant the patient complained of blurring and " transparency " (Figs. 2 to 7). In this part of the field the true colour was perceived, although it varied in intensity.

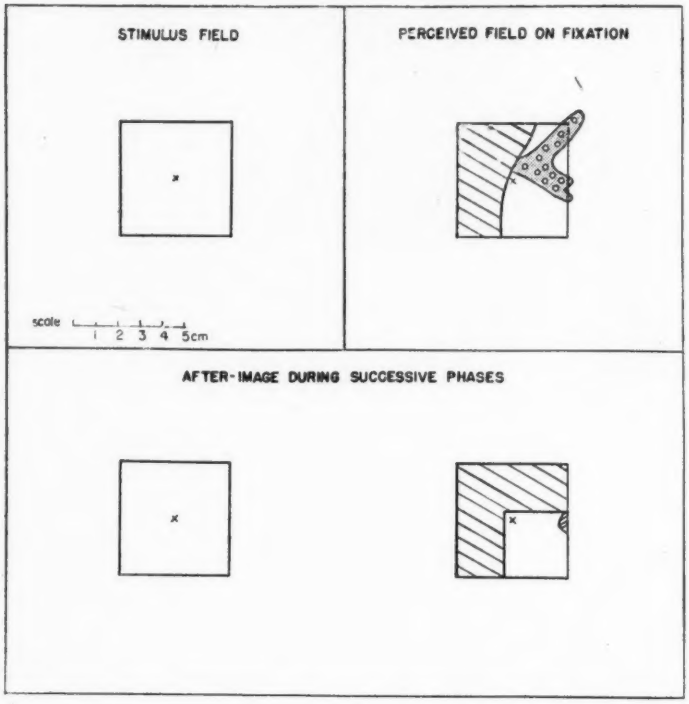

FIG. 2.—The basic pattern in series 1. *Stimulus field:* a 50 mm. square, with X indicating fixation point in centre of figure. *Perceived field:* indicated by unshaded part of square. Cross hatching part of the field not perceived on fixation. White dots on grey background is zone which appeared blurred or grey. After-image figures in legends as above.

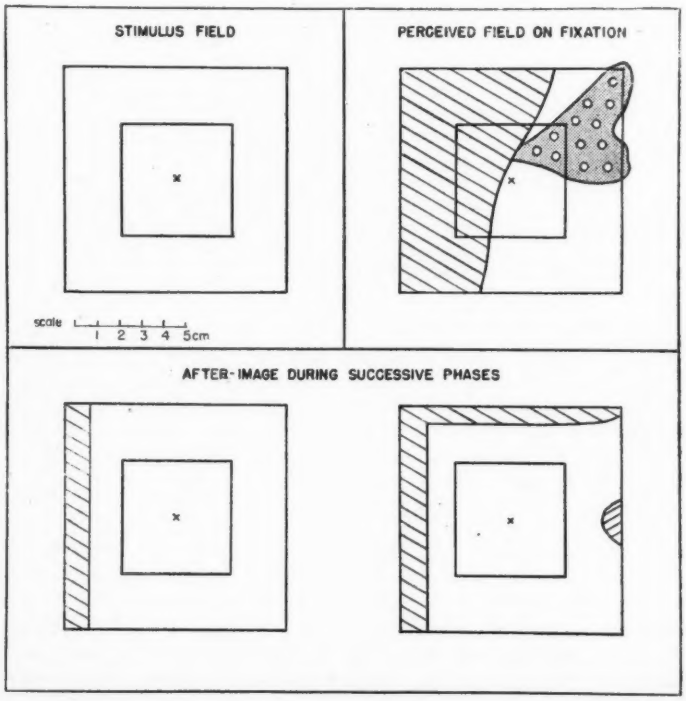

FIG. 3.—The basic pattern in series 2. *Stimulus field:* a 50 mm. green coloured square superimposed as illustrated on a 100 mm. red coloured square. Thus the green square was surrounded by a red border 25 mm. wide. Legends same as in Fig. 2.

After-Image.—On almost every test the figure seen in the after-image appeared to be greater in area than that noted during fixation of the stimulus field (phenomenon of completion). However, the areas in which "completion" occurred showed varying degrees of instability. In the completed regions there was fluctuation in intensity with waxing and waning of colours, while the colour and brightness of the rest of the after-image remained relatively constant. Frequently the patient reported that this part of the after-image appeared dim. In addition, a "grey shadow," insular in shape, appeared to the right of the fixation point completely obliterating the colour in this region of the after-image. The shape of the grey shadow, which corresponded to the relative scotoma elicited to the right of the fixation point on visual field tests, always had a clearly defined stable contour in contrast to the hazy shape of the faded-out border areas of the entire after-image. The visual after-image varied with the pattern used in the stimulus fields. This is illustrated on analysis of the following series.

Series 1.—In this group of tests the stimulus field consisted of single squares varying in size. A figure of either 50, 75, or 100 mm. square was presented in successive tests so as to determine whether the size of the stimulus field produced significant differences in the degree of completion of the figure in the after-image. The results showed that approximately the same amount of proportional completion was observed for each of the squares tested. Frequently almost the entire square was perceived in the after-image (Fig. 2). However, the left border of the figure at times appeared to be hazy and faded quickly. The right border was always clear. The extent of the area which appeared to be hazy in the after-image, which was always on the left side, was not fixed. It varied with the size of the stimulus presented. The larger the stimulus figure the greater was the absolute extensity of completion in the after-image.

Series 2.—In this group, 50, 75, and 100 mm. squares were again used in the stimulus field, but this time they were presented in various superimposed patterns. A smaller square (coloured green) was placed in the centre of a larger square (coloured red). Thus the stimulus fields consisted of a 50 mm. green square placed in the centre of either a 75 or a 100 mm. red square, or a 75 mm. green square was placed in the centre of a 100 mm. red square. The results in this group showed that the inner or smaller square was seen in the after-image always in its entirety. It was complete and showed stability, there being no parts missing and no fluctuation of the figure. In contrast to the strength and stability of the central square, the visible borders of the larger square tended to be slightly diminished in the after-image. At times the patient reported that he saw only one large square. There were no defects in the central regions of the after-image or in that which corresponded to the smaller square in the stimulus field. Characteristically the large complete square and the small complete square alternated in successive phases of the after-image.*

Series 3.—In this group the stimulus field consisted of four small squares arranged in a pattern to form a large square. They were spaced 5 mm. apart, subtending an area equal to a 50 mm. square; four 35 mm. squares spaced 5 mm. apart, subtending an area equal to a 75 mm. square; and four 45 mm. squares spaced 10 mm. apart, subtending an area equal to a 100 mm. square. The basic pattern is illustrated in Fig. 4.

In this situation the completion effect in the after-image appeared independently in each of the small squares. The results were comparable to those obtained with presentation of only one square at a time in each of the quadrants. Under these conditions there was never an after-image in the left superior quadrant of the field. In the remaining three quadrants the patient saw images of the squares, parts of which he could not see in the stimulus field (Fig. 4). At different times he reported that he saw three or two squares. He never saw the composite of four squares on a background in the after-image. The squares on the right side, especially the one in the right lower quadrant, were always seen in the after-image.

The after-images of the four squares also varied in regard to latency, intensity, and duration. In the right inferior quadrant the duration and stability of the after-image was more than in any other part of the field; the squares in the right superior and left inferior quadrants appeared somewhat later, were less vivid, and did not last as long as the one in the right lower quadrant.

Series 4.—In this group the stimulus field consisted of four small squares on a large square of a different colour, usually green on red. The basic pattern is illustrated in Fig. 5. Four 22·5 mm. squares were placed in the centre of either 75 or 100 mm. squares of a different colour, or four 35 mm. squares were

* Although nominally the entire stimulus pattern can be regarded as the figure, and the white field on which the pattern is placed as the background, figure-ground differentiation can also be made within the stimulus pattern itself when squares of different colours are presented symmetrically around the fixation point. One cannot arbitrarily assert that either the smaller or the larger square is the figure. The alternation of the perception of the squares in the after-image suggest a parallel to Rubin's reversible figures. There may be rivalry between the differently coloured squares, each alternating at being the figure, while the other is the ground, and consequently dominant in the after-image for a short period.

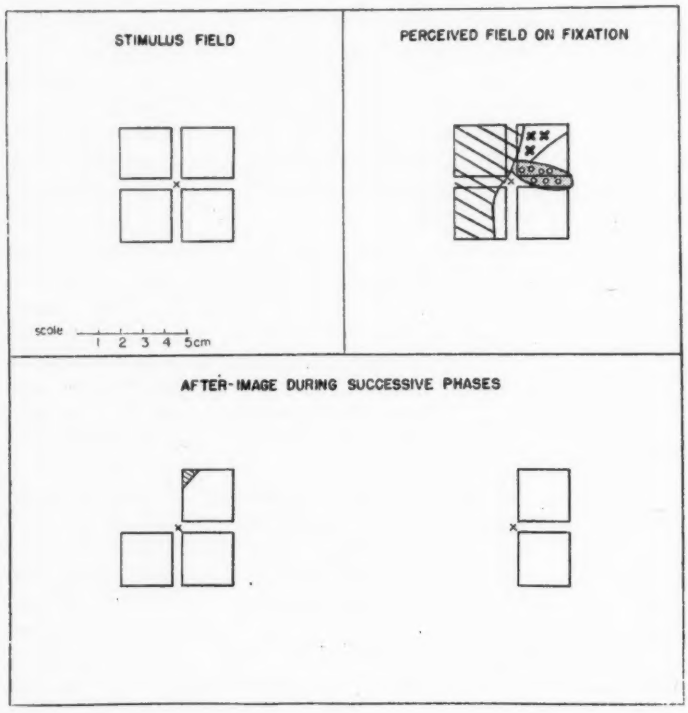

FIG. 4.—The basic pattern in series 3. Four 22·5 mm. green squares spaced 5 mm. apart so that the total area of figure is equal to a 50 mm. square. Area in right upper quadrant shaded with X indicates region in which colour of after-image appeared dim. Rest of legends as in Fig. 2.

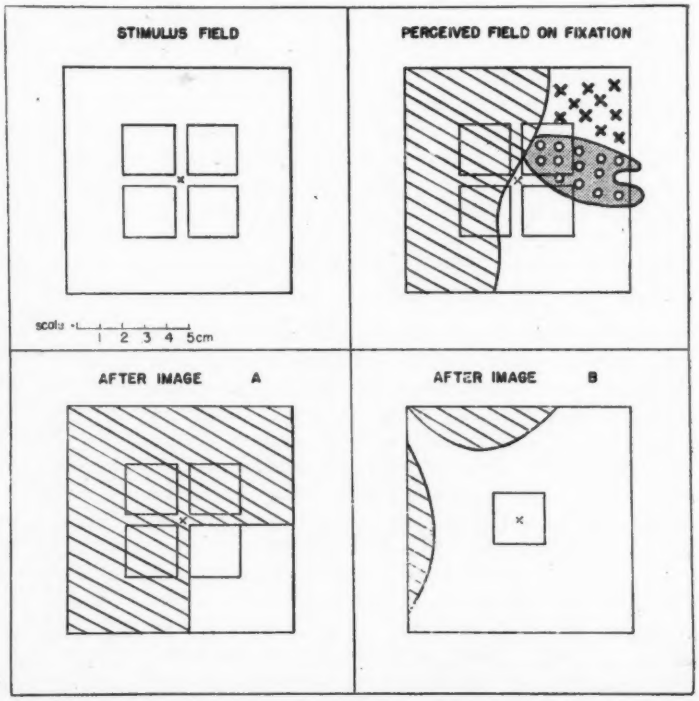

FIG. 5.—The basic pattern in series 4. Four 22·5 mm. green squares arranged within a 50 mm. square area and superimposed on a 100 mm. red square. Legends same as above.

superimposed on a 100 mm. square of a different colour. With these test patterns there seemed to be a decrease in the extent of the total area occupied by the after-image. Only a small part of the perceived field (that in the right lower quadrant) appeared in the after-image. Nevertheless, that part of the stimulus figure which appeared in the after-image tended toward completion. For instance, the patient reported that he saw an entire square in the after-image whereas in the stimulus field he saw only part of the square. At times the one small square he saw in the right lower quadrant of the stimulus field appeared in the after-image as the central figure, with the large continuous square serving as the background. Here it seemed as if the small square perceived in the right lower quadrant of the stimulus field were apparently " displaced " toward the centre when seen in the after-image. On other occasions this square was " displaced " to a position just downward and to the right of the fixation point in the after-image.

Series 5.—In a variation of the last series, the stimulus field in this group consisted of smaller coloured squares superimposed at the corners of the larger square of a different colour, usually green on red. The basic pattern is illustrated in Fig. 6. Under these conditions there was a much greater tendency to see a uniformly coloured single large square in the after-image. After a variable latency the patient reported that he saw one or more of the small squares. The small squares, however, varied in latency of appearance and intensity of colour.

There were also several instances of apparent "displacement " in this series. The small squares in the right side corners were displaced diagonally toward the centre (Fig. 6). In one instance, only the right lower square was seen, and it was " displaced " horizontally toward the mid-line.

Series 6.—In this group the stimulus field consisted of a single coloured square superimposed on a larger field of four single squares of a different colour, usually red on green. The basic pattern is illustrated in Fig. 7. A 50 mm. square was superimposed on either four 35 mm. or on four 45 mm. squares ; a 75 mm. square was superimposed on four 45 mm. squares. In the after-image the patient saw the entire stimulus pattern on two occasions. However, parts of the two outer squares on his left were indistinct or faded quickly. There were also further instances of displacement, but this time in a centrifugal direction. It can be seen in Fig. 7 that the discontinuous squares were displaced peripherally and were seen as almost complete squares.

Discussion

Our data show that the visual after-images in a patient with defective fields of vision vary with conditions of testing. In most instances the after-image shows completion. There is an increase in the extent of the figure over that perceived in the stimulus field.

These studies show that completion effects depend to some extent on the stimulus figure. Size and configuration of the presented pattern are some of the factors which determine completion. Increase in the size of a given stimulus pattern (such as a square) can produce a greater extent of completion (series 1). On changing the configuration within the stimulus figure (square) but keeping the contour and area constant (such as dividing the square as illustrated in Fig. 2 into four quarters as illustrated in Fig. 4) the degree of completion is decreased.

In comparing results in series 1 and 2 with series 3, it can be seen that when the stimulus figure is simple and continuous in contour, such as a single square (Fig. 2 in series 1, Fig. 3 in series 2) there is a greater extent of completion than when the stimulus figure is discontinuous, such as a composite of four small squares (Fig. 4 of this series).

Explanations for completion effects in visual after-imagery and in tachistoscopic studies have been offered by the Gestalt school. They postulate that the qualities of the figure in the stimulus field might be partly responsible for the phenomenon of completion. Some of the qualities they consider as primary in perception are " goodness," " continuation," and " closure " of the figure.* According to Koffka (1935) (after Wertheimer) " psychological organization will always be as " good " as the prevailing conditions will allow."

It is well known that in normal subjects the figure in the stimulus field may undergo changes in the after-image. Thus the after-image of a square might gradually lose its sharp corners and become more and more circular. Rothschild (1923) found that the occurrence of an after-image itself depended on whether it made a " good " shape or not ; that if the contours in the stimulus figures were " good," or formed a simple shape, such as a square or a circle, they produced satisfactory after-images, even

* By " goodness " of the figure the Gestalt psychologist means the ease with which a figure can be perceived under certain conditions. For instance, a circle at high speeds of exposure can be recognized more readily than a figure of irregular outline. The concept of " goodness " includes such figural properties as regularity, symmetry, and simplicity, as in a square, circle, and similar geometric figures. By " continuation " the Gestaltists imply that the perceiving subject adds features to a repetitive pattern. Thus if a wavy line is presented and the last wave is incomplete, the subject would report a complete wave. By " closure " is meant the tendency of a subject to report a simple pattern (such as a circle) as complete even though there was a small gap in the stimulus figure. For greater details see Koffka (1935). In addition they consider the factors of internal organization of the figure and the relation between figure and back-ground.

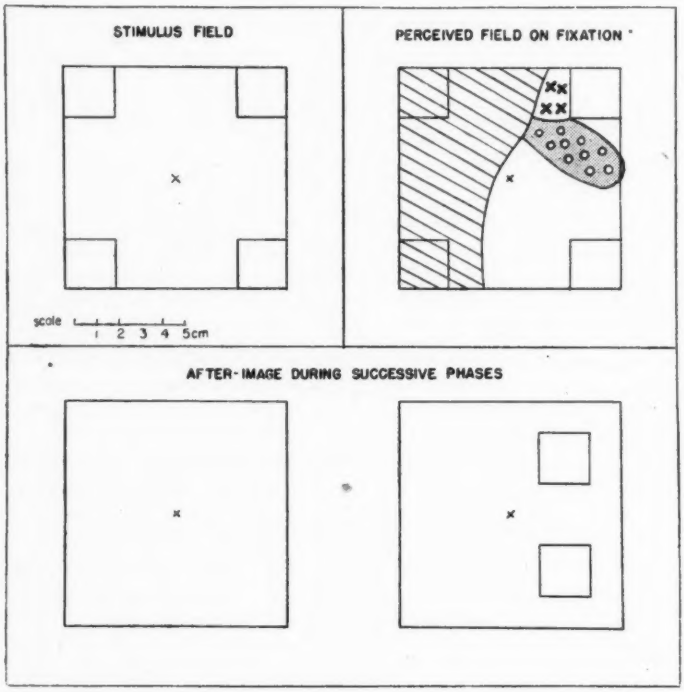

FIG. 6.—The basic pattern in series 5. Small green-coloured squares 22·5 mm. placed in each of corners of a 100 mm. red coloured square. Legends as above.

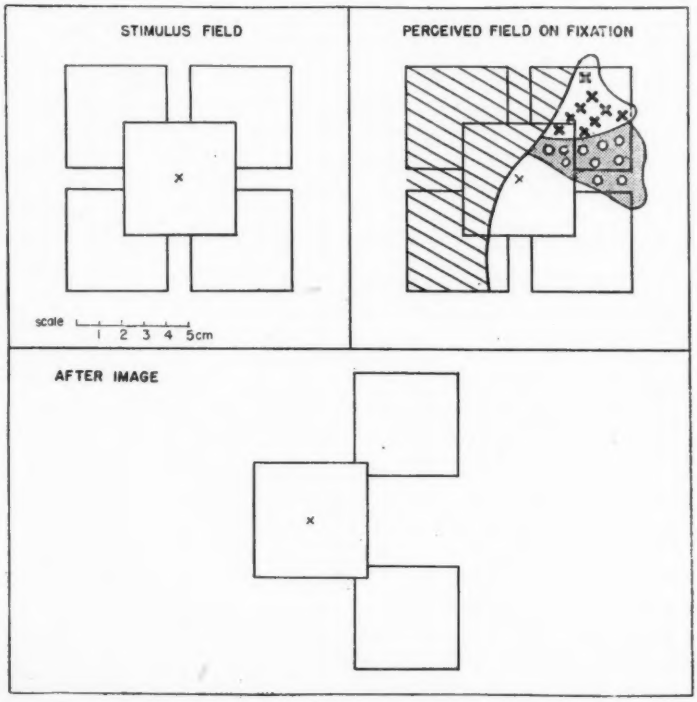

FIG. 7.—The basic pattern in series 6. One 50 mm. green square superimposed on four 45 mm. red squares. Total area of stimulus field 100 mm. square.

improving on the originals (stimulus figures) inasmuch as all slight irregularities would disappear. If, on the other hand, the lines of the stimulus figure did not form a simple shape, such as an irregularly shaped square or circle, the after-image would either be a " better " shape or several of the lines would not appear in the after-image. Frank (1923), Shibata (1936), and Schottlaender (1936) have reported changes in the after-image as a function of the figural qualities of the after-field (the stimuli applied to the retina during the experience of the after-image).

According to Fuchs (1920, 1921) completion can also occur when there is sufficient perception on fixation to determine the " law " of the entire figure. In Gestalt terms a figure can be said to have a law when it is organized in a highly stable fashion, that is, if it is characterized by the properties of " goodness." It is then only necessary for the observer to perceive enough of the figure to allow the " internal organizing forces " to become established in order for completion to occur. In our case the patient perceived squares or the greater part of a square. The law of the figure was a square.

From other findings in our case it would seem that the completion effects noted in the after-images might illustrate such a Gestalt principle as " closure." The filling-in in the after-image of areas of relative scotoma and the completion of gaps in the contour of the figure perceived in the stimulus field might serve as an example of closure. Unfortunately our studies were not very exhaustive. The patient's continued poor health did not permit us to make all the tests which we would have liked. Hence we do not have sufficient data to support the theory that figural qualities alone are responsible for the phenomenon of completion in visual after-images.

Our results also revealed that the after-image of a figure may be considerably enhanced when there is a background or surrounding field of stimulation. This was shown in series 2 (Fig. 3), in which a smaller enclosed figure was more completely seen and possessed more stability than when shown alone. This phenomenon has been previously noted by Koffka, and also appears to be related to the findings summarized by Bartley (1941), in which a surrounding border influenced the differential brightness threshold of central areas. Apparently the presence of a surrounding field has an effect on the gradient of function of the enclosed figures.

Besides completion, the after-images in our case showed variation in latency, intensity, and duration. On testing each of the four quadrants of the perceived field it was found that the after-image of a figure studied in the left lower or in the right upper quadrant appeared after a longer latency, was lighter in colour, and faded more quickly than the after-image of figures which were exposed in the left upper quadrant. It is well known that latency, intensity, and duration of the after-image in normal as well as pathological subjects may vary from one examination to another. It is also known that these variables are systematically altered in patients with cerebral lesions (Brückner, 1917 ; Vujic and Levi, 1939 ; Ruesch, 1944). However, the changes noted in our case were consistently greatest in the affected quadrants. In the patient's normal right lower quadrant of the perceived field the variations in latency, intensity, and duration were minimal. Since these changes always occurred in a certain part of the after-image field they might assume clinical significance. On using this method in other cases it was found that decrease in intensity and duration and increase in latency occurred consistently in homonymous parts of the after-image field of each eye. In fact, in some cases the method of after-imagery demonstrated a defect in the homonymous fields which routine perimetry failed to disclose. On the other hand, due to the occurrence of completion, visual after-imagery cannot be substituted for the perimetric method. Williamson (1945) advocated visual after-imagery as a quick method for determination of defects in fields of vision, but he did not take into account that after-imagery often reveals a lesser defect than does campimetry.

In conclusion it is evident that a study of the fields of vision by the method of visual after-imagery yields information which other methods such as perimetry and tangent screen examinations fail to reveal. Although the changes elicited on visual after-imagery are frequently variable, they are still significant inasmuch as they occur consistently in a given part of the field. They can be found within, and adjacent to, parts of the field of vision which seem to be defective. Moreover, the changes conform to a pattern and occur in homonymous parts of the visual after-image of each eye. The pattern of the after-image field is determined by the fixed relation between the apparently defective and normal parts of the fields of vision.

Summary

1. Completion effects (an increase in the extent of the figure in the after-image over that in the perceived field) in the visual after-image of a patient with homonymous scotomas were studied by varying the geometric pattern within the stimulus field.

2. The size and configuration of the stimulus figure, as well as the presence of a surrounding field of stimulation, are some of the many factors which

alter the visual after-image and lead to completion.

3. Consistent changes in latency, intensity, and duration can be shown in homonymous parts of the after-image field, whereas the corresponding regions in the perceived field show no defects.

4. Visual after-imagery can be used as another method of demonstrating defects in field of vision. On the other hand, due to completion effect, visual after-imagery cannot be substituted for the perimetric or any other method of testing vision.

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VISUAL SCOTOMATA WITH INTRACRANIAL LESIONS AFFECTING THE OPTIC NERVE

BY

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Central or paracentral scotoma is an occasional manifestation of certain space-occupying intracranial lesions. The reason for the development of this defect is not yet clear.

Traquair (1946) defines a scotoma as " an area of depressed vision within the field margin surrounded by an area of less depressed or normal vision." Either a depressed area or a channel of varying width may connect the scotoma with the periphery or with the blind spot or with both. Extension of a scotoma to the margin of the field is referred to as " breaking through." When such an extension has occurred careful quantitative perimetry will determine to what extent the central defect predominates in the visual field.

Sudden consciousness of failing vision usually indicates a macular defect, and may bring the patient to an ophthalmologist before pallor of the discs has developed. Bitemporal defects are of gradual onset, and as about 120 degrees of the binocular field remain unaffected the patient's orientation is not seriously disturbed. Hence, except in the case of retrochiasmal lesions when pallor of the disc may never appear, patients whose macular vision is good do not present themselves for examination until they have reached the stage when pallor of one or both discs is evident.

Theories Explaining Scotomatous Defects

Several theories have been put forward to explain scotomatous defects.

Retrobulbar Neuritis

Foster Kennedy (1916), when referring to the syndrome described by Paton in 1909 and by himself in 1911 stated that this consisted of " the occurrence of a true retrobulbar neuritis with the formation of a central scotoma and primary optic atrophy on the side of the lesion, together (if the pressure be sufficiently great) with ipsilateral anosmia and papillœdema in the opposite eye."

Larsson and Nord (1947) called attention to the " well-known fact " that the clinical picture of retrobulbar neuritis, consisting of failing vision and central scotoma with or without ophthalmoscopic changes, may be caused by pressure of an expanding intracranial lesion upon the optic nerve in its prechiasmal course. Recently Woods (1948) mentions " intracranial lesions—suprasellar tumours and so forth " as being among the more frequent causes of retrobulbar neuritis.

Vulnerability or Hypersensitivity of Macular Fibres to Pressure

Jefferson (1945) stated " that we should abandon any further mention of retrobulbar neuritis, a difficult enough pathological concept without invoking it unnecessarily. Clearly the cause of the scotoma and of the optic atrophy is plain compression and most ophthalmologists are agreed about the special vulnerability of the macular fibres." Kestenbaum (1947) stated, " If the optic nerve is compressed for any reason anywhere in the orbit, in the optic canal or within the cranium, almost always a central scotoma develops. The reason for this phenomenon is still questionable, hypersensitivity of the highly-specialized macular fibres or depleted blood supply (Behr, 1935) have been considered most likely." Peter (1931) wrote, " It is well known that the papillo-macular bundle is more susceptible to toxic or to pressure influence than any other parts of the nerve."

The opinions just quoted imply that pressure on any part of the optic nerve will produce a central scotoma. There are, however, many cases in which the optic nerves appear to be subject to pressure and in which there are no defects of central vision.

In the most common type of pituitary tumour the optic nerves appear to be whiter than normal, to be flattened, and to curve round the tumour tightly embracing it. The expanding tumour must have exerted a considerable amount of pressure to produce such distortion, yet a central scotoma in such a case is a rarity. Before the fields have advanced beyond the stage of bitemporal hemianopsia either the maculæ are spared or they are split by a bitemporal hemianopic scotoma. A meningioma of the tuber-

culum sellæ produces the same distortion of the optic nerves and the same hemianopic defect. It is difficult to reconcile the obvious pressure on the nerves with the absence of central scotoma if the macular fibres are specially vulnerable. Central scotomata of course do occur, but when they occur the relationship of the tumour to the nerves is not that outlined above.

It has been suggested that upward pressure on an optic nerve against the anterior cerebral artery may be a factor in the production of scotomatous changes. McConnell and Mooney (1938) reported cases in which there was gross notching of the optic nerves by the anterior cerebral arteries and in which there was neither an inferior altitudinal defect nor a scotoma. Fig. 1 illustrates a definite groove in the optic nerve from which the anterior cerebral artery

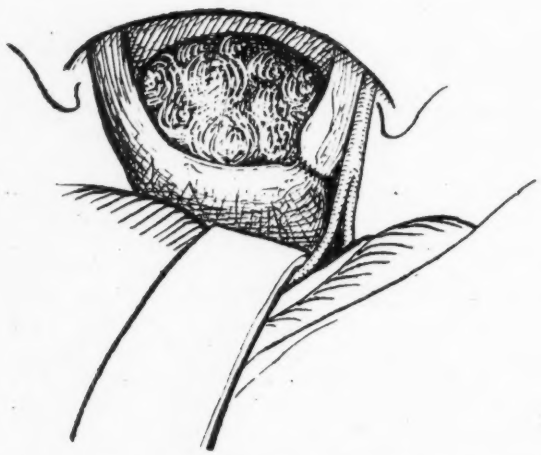

FIG. 1.—Groove on the dorsal surface of the right optic nerve caused by pressure against the anterior cerebral artery.

has been raised, and Fig. 2 shows the visual fields in the same case. Involvement of the macular fibres would appear inevitable in a case of this kind, especially if they were hypersensitive.

Henderson (1939) suggested that acute angulation of the optic nerve against the upper margin of the optic foramen might affect only the macular bundle of fibres and that such an effect could be due to a lateral protrusion of a pituitary adenoma.

Jefferson (1940) depicted acute elevation of the optic nerve close to the optic foramen in a patient with a large extension of a pituitary adenoma into the temporal lobe. In the corresponding eye " vision was lost except for a crescent which ran across the superior temporal and nasal quadrants. Macular vision was lost." The pituitary tumours which are associated with unilateral central scotomata appear to be those which insinuate themselves below the nerve close to the optic foramen, thus pushing the nerve upwards.

It is well known that tumours such as olfactory groove meningiomas which exert pressure on the optic nerve immediately behind the optic foramen tend to be associated with central scotomata. There is however no constant relationship between the incidence of central scotomata and the displacement of the nerve. Jefferson (1937) reported two cases in which an aneurysm was demonstrated just behind the optic foramen. In each case the nerve was acutely raised and stretched over an aneurysm : in one case there was a central scotoma, in the other a hemianopic defect. Perusal of the literature leaves the impression that central scotomata are particularly liable to occur when a tumour is so situated that it either raises or depresses the optic nerve close to the optic foramen. Such pressure at this point pushes the nerve against a rigid structure, the upper or lower edge of the optic foramen. As at this point the macular fibres form an axial core it is necessary to invoke the doctrine of hypersensitivity to explain their involvement.

INTERFERENCE WITH THE BLOOD SUPPLY OF THE OPTIC NERVE

Traquair (1946) wrote, " Anatomical conditions in connexion with the blood supply probably have an important influence as well as special susceptibility of the macular fibres." He suggested that pressure on the surface of the nerve might disturb the nutrition of the underlying fibres by obstructing their vascular supply, and that conduction interference and optic atrophy might be initiated in this way, rather than by the effect of pressure on the fibres themselves.

Vail (1948) in a review of recent work on the blood supply of the optic nerve states that the intracranial part of the optic nerve is supplied by branches from the internal carotid, the ophthalmic, the anterior cerebral, and the anterior communicating arteries. " The minute vessels penetrate the pia, pass into the nerve tissue, and form the septal network of the nerve." In the axial portion of the nerve " in which the papillo-macular bundle is situated, the septa are thinner and more scarce (the " end-arteries " of Magitot) than in other places, and the individual optic-nerve bundles are thus larger. The nutrition of the papillo-macular bundle is therefore less abundant in the intracranial part of the optic nerve than elsewhere." The intracanalicular portion of the optic nerve is supplied by the ophthalmic artery, and in this portion also the pial network is relatively poor (Wolff, 1948).

These anatomical studies suggest that any im-

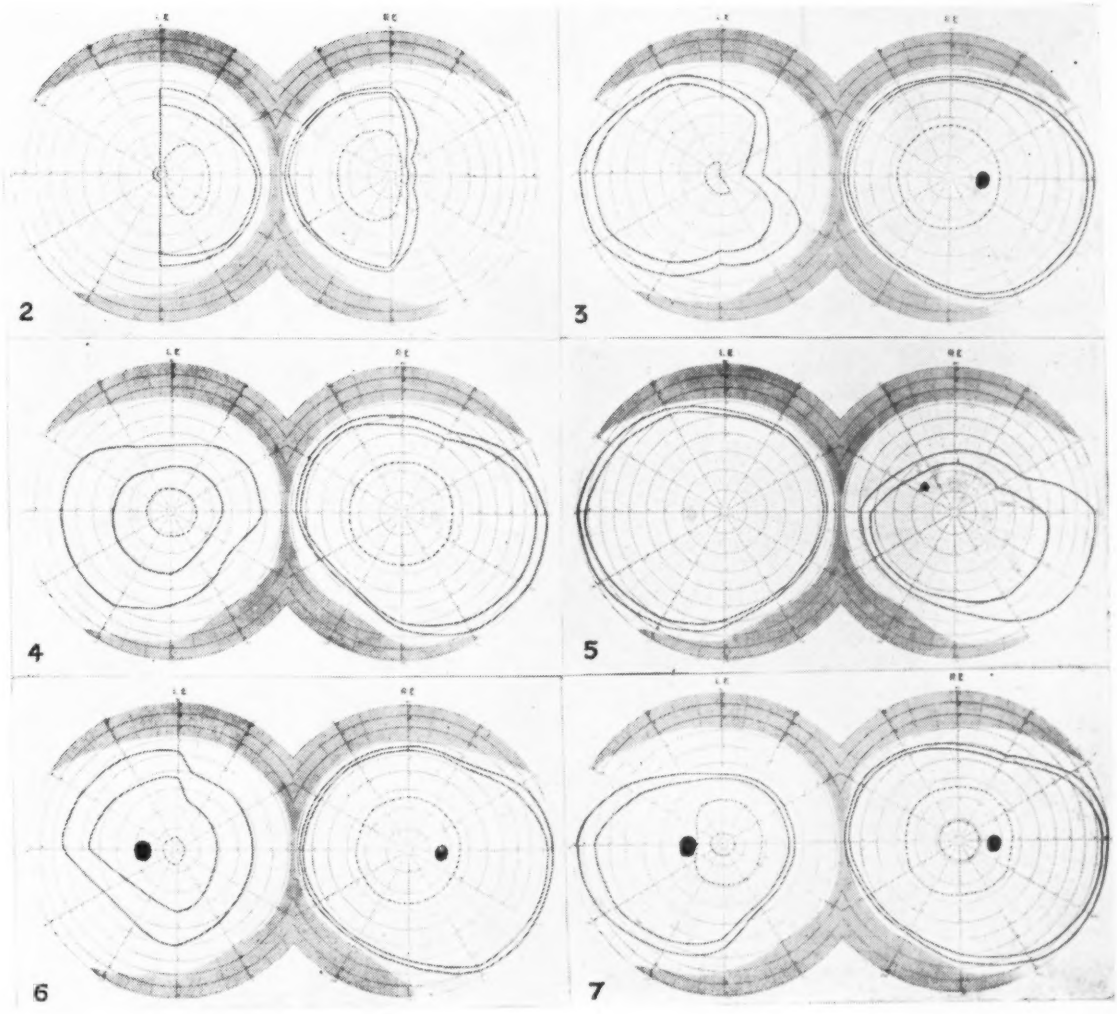

FIG. 2.—Visual acuity : both eyes, 6/6. Objects : 3/330, 1/330, 2/2000.

FIG. 3.—Visual acuity : right eye, 6/5 ; left, 6/12. Objects : 3/330, 1/330, 2/2000.

FIG. 4.—Visual acuity : both eyes, 6/5. Objects : 3/330, 1/330, 2/2000.

FIG. 5.—Visual acuity : right eye, 6/9 ; left, 6/5. Objects : 3/330,1/330.

FIG. 6.—Visual acuity : right eye, 6/6 ; left, 6/18. Objects : 3/330, 1/330, 2/2000.

FIG. 7.—Visual acuity : right eye, 6/5 ; left, 6/6. Objects : 3/330, 1/330, 2/2000 (white) ; 5/2000 (red).

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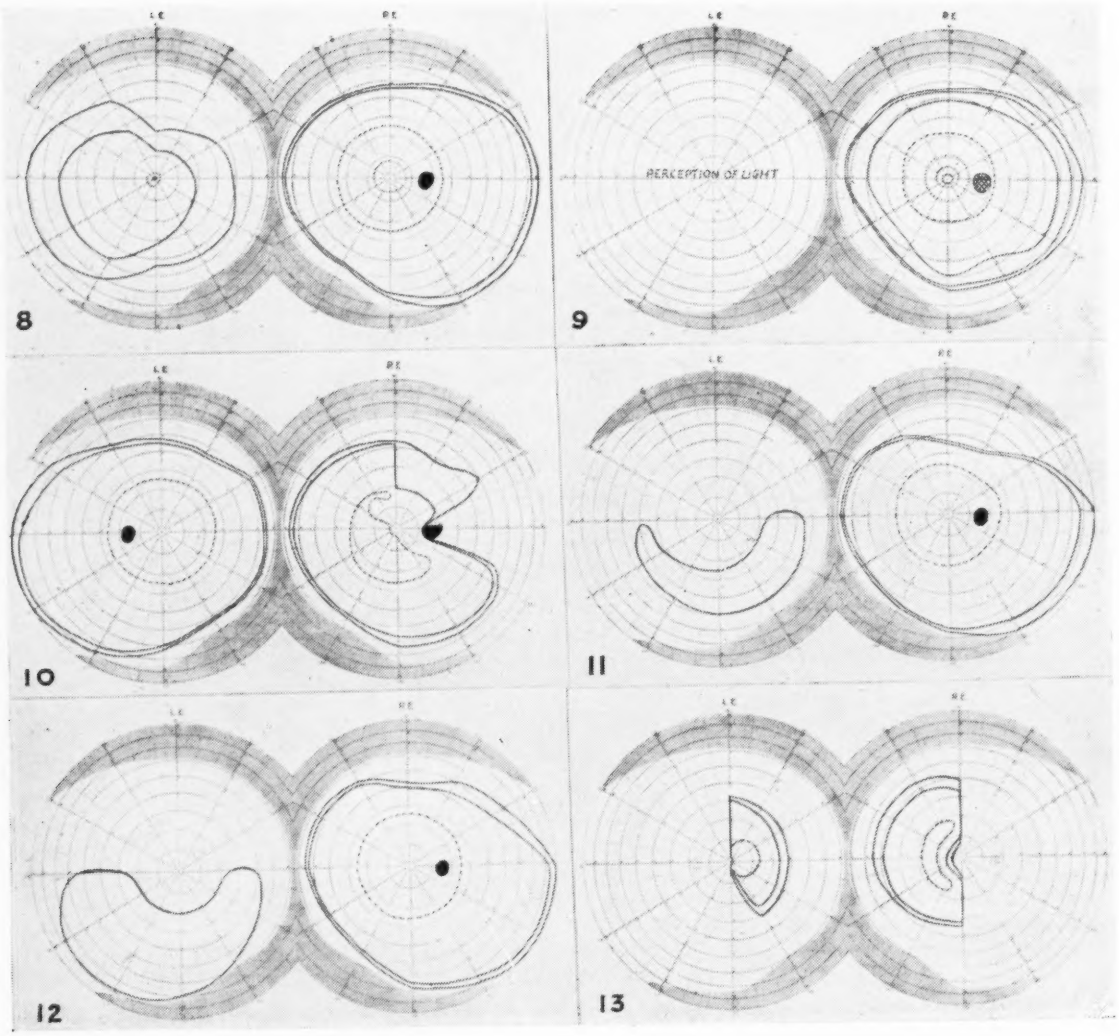

FIG. 8.—Visual acuity : right eye, 6/5 ; left, 6/36. Objects : 3/330, 1/330, 2/2000, 5/2000 (white), 5/2000 (red).

FIG. 9.—Visual acuity : right eye, 6/6 ; left, perception of light. Objects : 20/330, 3/330, 1/330, 10/2000, 3/2000 (white), 10/2000 (red), 5/2000 (red).

FIG. 10.—Visual acuity : right eye, 6/60 ; left, 6/6. Objects : 3/330, 1/330, 2/2000.

FIG. 11.—Case 1. Visual acuity : right eye, 6/5 ; left, hand movements. Objects : 3/330, 1,330, 2/2000 ; left eye, 20/2000.

FIG. 12.—Case 1. Visual acuity : right eye, 6/5 ; left, perception of light. Objects : 3/330, 1/330, 2/2000 ; left eye, 20/2000.

FIG. 13.—Case 2. Visual acuity : right eye, counts fingers at 2 feet ; left, 3/60. Objects : 3/330, 1/330, 2/2000.

pairment of the circulation in the intracranial or canalicular portion of the optic nerve would affect the macular bundle more than it would affect other fibres.

It is generally assumed that the field defects following optic-nerve trauma are due to tearing of the pial vessels. As the ischæmia in these cases might not be unlike that due to pressure on the pial vessels from without by a swelling such as a tumour, a short account of the field defects following trauma appears to be relevant.

Hughes (1943) said that he was coming more and more to believe that most field defects were, in fact, due to embarrassment of the vascular supply of the nerve or chiasma as the case might be. " Perhaps it might be possible to explain the diminished conduction in the nerve fibre on a vascular basis, whereas it would be difficult to do so on the basis of direct compression of the fibre." He (1945) states that there are two features in the typical group of field defects following traumatic lesions of the optic nerve ; one, a constant feature, is an inferior altitudinal defect ; the other is general depression. In one case only of seventeen reported by this author was a " pericentral " scotoma present.

Turner (1943), in a study of thirty-three cases, found that the visual field defects after partial injury to the optic nerve fall into two main groups, " The first in which a scotoma is the leading feature, the second in which a peripheral sector defect is outstanding." In the scotomatous group there were eight cases, in three of which the scotoma was pericentral, in four paracentral, and in one cæco-central. In Turner's thirty-three cases there were therefore only three with a *central* scotoma. Whatever the changes in the peripheral field it seems correct to say that a central scotoma is not a common feature in traumatic lesions of the optic nerve. In Mooney's (1945) series of eight cases of optic nerve injury (Figs. 3 to 10 inclusive) the visual defects were predominantly peripheral, and in the only two cases (Figs. 8 and 10) with macular involvement the retinal arteries were narrower than those of the opposite eye. The latter finding suggests that pericentral defects are due to involvement of the recurrent branch of the central artery of the retina.

As involvement of the pial branches of the ophthalmic artery by trauma does not affect the papillo-macular bundle with any constancy, it is not clear why local involvement of these vessels by pressure from a tumour should have that effect. Traquair pointed out that it was not the position of the tumour but the position of damage to the circulation that would produce field changes.

The possibility that the blood supply of the optic nerve might be impaired by pressure on the ophthalmic artery itself occurred to one of us (A.M.) when inspecting an arteriogram in the following case :

Case 1.—A man aged 28 years was admitted to the Richmond Hospital, Dublin, on Dec. 4, 1946. In July 1945 he had had an attack of severe pain in the left eye. This continued for a few days. In March 1946 he had a similar attack and then he noticed that the vision of the left eye was impaired. From that time vision of this eye deteriorated steadily.

FIG. 14.—Case 1. Arteriogram of the left internal carotid artery showing widening of the carotid curve.

The patient was a typical acromegalic. Radiographic examination revealed gross destruction of the pituitary fossa with disappearance of the clinoid processes and the roof of the sphenoidal sinus. General neurological examination was negative.

Dec. 9, 1946.—The findings on ophthalmic examination were : visual acuity in right eye 6/6 (Snellen) ; left eye, hand movements only ; discs normal. The left pupil reacted sluggishly to light. Perimetry showed slight flattening of the isopters in the upper temporal quadrant

of the right eye and in the left eye a large central scotoma which had broken through above (Fig. 11). The discrepancy between the gross central defect in the left eye and the minimal peripheral defect in the right, so rare with pituitary adenomas, suggested the possibility of an aneurysm, in spite of the characteristic clinical features. Perabrodil was injected into the left common carotid artery. The arteriogram did not reveal an aneurysm but it showed the curve of the carotid syphon to be greatly modified (Fig. 14). The distal curve appeared to be widely opened out and the supraclinoid portion of the artery to be higher than normal. The appearance suggested that the tumour had extended laterally inside the natural curve of the artery. It seemed that such a displacement of the internal carotid artery might possibly kink or partially obstruct the ophthalmic artery at its origin or occlude some of the minute branches which it gives off in this region. Some of these branches may be destined to supply a section of the papillo-macular bundle.

As this patient was submitted to deep radiation therapy there was no opportunity to verify the surmise by direct inspection.

Oct. 11, 1948.—Ophthalmic examination showed visual acuity, right eye 6/5 (Snellen); left eye counts fingers close to his face. Right field unchanged; left field, large central scotoma with normal lower peripheral field to hand movements (Fig. 12).

It so happened that when this patient was under observation an operation was performed on another patient with a large central scotoma, and an elevation of the internal carotid artery was demonstrated.

Case 2.—A man aged 33 years was admitted to the Richmond Hospital, Dublin, on Dec. 4, 1946. Nine months previously he had begun to suffer from headaches, which became steadily more frequent and severe. About the same time he noticed that his sight was becoming poor. The skin of his face was smooth and hairless. No genital deformity was noted. General examination was negative and there were no abnormal neurological signs apart from the visual defects. Radiographic examination showed that the dorsum sellæ had been eroded and that there were slight but definite supra- and intra-sellar calcification.

Ophthalmic Examination.—The visual acuity was: right, counting fingers at 2 feet; left, 3/60 (Snellen). The right disc was normal, the left pale with clear margins and normal vessels. Perimetric examination revealed bitemporal hemianopsia for 3/330, 1/330, and 5/2000, white, with a large central scotoma on the right side and a small one on the left for these visual angles (Fig. 13).

Dec. **6,** 1946.—An operation for right frontal craniotomy was performed. When the right optic nerve was exposed it was seen to rise abruptly from the optic foramen and to pass to the temporal side. Further exposure showed that its acute elevation was due to a soft cystic tumour which also filled the pituitary fossa and appeared to overflow the left dorsal surface of the chiasma (Fig. 15). Aspiration of 6 ml. of oily fluid allowed the right optic nerve to become relaxed and flat, and the right carotid artery which had been concealed by the displaced nerve was seen to lie on the upper aspect of the cyst. The left optic nerve was displaced laterally but was not grossly elevated. A wide opening was made in the cyst wall and a considerable amount of gelatinous tumour was removed with a curette. The tumour extended backwards under the chiasma but no attempt was made to discover its posterior limit. The Pathological report diagnosed a craniopharyngioma.

Jan. 15, 1947.—Ophthalmic examination showed marked recovery in the fields. Both presented the appearance of moderate general depression for the larger isopters with bitemporal hemianopsia for 10/2000; red (Fig. 19).

Comment.—The gross central scotoma in this case seemed to be unrelated to the bitemporal

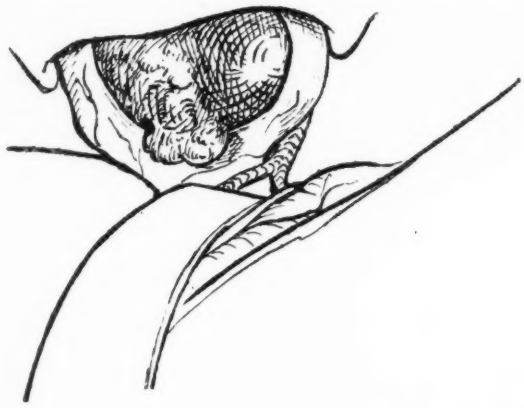

FIG. 15.—Case 2. Craniopharyngioma with large cyst elevating the right optic nerve.

hemianopsia. The latter could be explained by pressure on the medial aspects of the optic nerves or by involvement of the chiasma, but the former demanded some other explanation. The association in two cases of a large central scotoma with the same kind of variation in the appearance of the internal carotid artery led to a study of the anatomy of the opthalmic artery.

The ophthalmic artery comes off the *medial* side of the upper aspect of the internal carotid artery at its last bend. It then passes across the convexity of the artery between it and the optic nerve before coming to lie on the lateral side of the nerve (Fig. 16).

The relationships of the internal carotid artery, the ophthalmic artery, and the optic nerve close to the optic foramen appear to be such that any severe pressure on the optic nerve from above would necessarily be transmitted to the ophthalmic artery; and any pressure on the internal carotid artery

from below would press the ophthalmic artery against the nerve and both against the falciform fold which forms the upper edge of the optic foramen. In either event what would be seen during the operative exposure would be the nerve depressed by something above it or the nerve raised and stretched by something below it. In both cases the ophthalmic artery would be concealed by the optic nerve. We had noted an elevation of the internal carotid artery on previous occasions but had not attached any significance to it as the obvious deformity of the optic nerve seemed to be a sufficient explanation of the scotomatous defect.

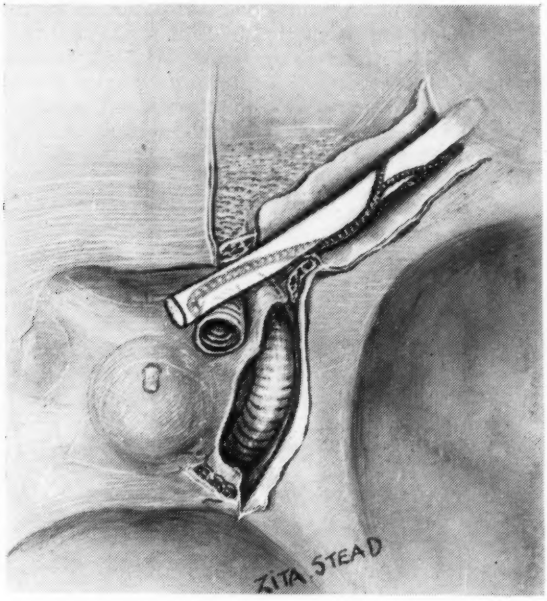

FIG. 16.—From a dissection to show the origin and course of the ophthalmic artery. The nerve is represented as transparent. The roof of the optic canal has been removed and the dural sheath opened.

The following case is an example :

Case 3.—A man aged 56 years was admitted to hospital on Oct. 22, 1937. He stated that his left ear had become deaf in 1928 and that in 1935 the left eyelid drooped and the eye turned upwards. Four months before admission he found that the vision of the left eye had nearly disappeared. There had been a complete absence of pain or numbness.

On examination there was ptosis of the left eyelid with mild exophthalmos ; the left pupil was smaller than the right and reacted sluggishly to light. Visual acuity was : right, 6/5 (Snellen) ; left, counting fingers at one metre. The right disc was normal ; the left was pale with clear margins and normal vessels.

Oct. 24, 1937.—The right eye was normal. The left eye had a large cæco-central scotoma for 40/2000, breaking through for 5/2000 and 2/2000, white. There was slight general depression (Fig. 20).

Oct. 28, 1937.—At operation a large left transfrontal exposure was made. The optic nerve was found running in a normal direction but both it and the internal carotid artery were elevated upwards about $\frac{1}{2}$ cm. behind the optic foramen and seemed to be riding over the surface of a tumour. The dura of the middle fossa was found to be lifted up to the level of the sphenoidal ridge (Fig. 17).

Incomplete removal of meningiomatous tissue was effected from the left middle fossa. Some tumour was scooped out from beneath the left optic nerve but at the conclusion of the operation the nerve and vessel had not assumed normal levels.

Nov. 14, 1937.—Examination showed slight left-sided exophthalmos. The fundi were unchanged. Visual acuity was : right, 6/5 (Snellen) ; left, 3/60 (Snellen).

The visual field of the right eye was normal. In the left eye the cæco-central scotoma for 40/2000, white, had disappeared. There was some recovery in the 5/2000, and 2/2000 isopters. The general depression was less marked (Fig. 21).

In the two verified cases just reported (Cases 2 and 3) the maximum pressure on the optic nerve and internal carotid artery seemed to be exerted close to the optic foramen, the tumour undermining the anterior clinoid process. In the unverified case

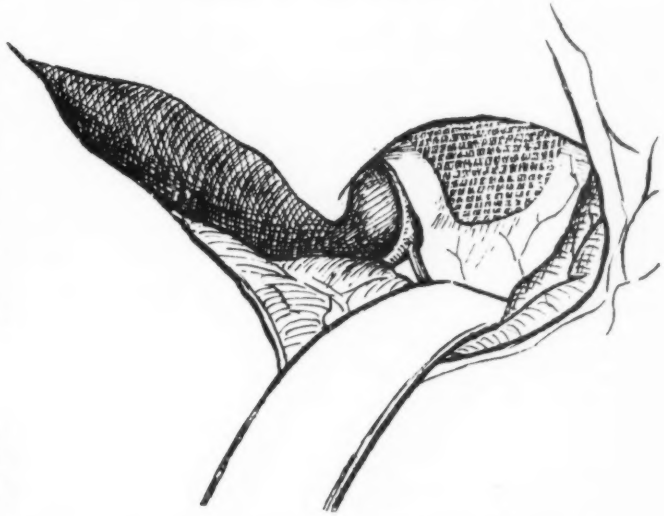

FIG. 17.—Case 3. Meningioma of the middle cranial fossa passing medially under the internal carotid artery and the left optic nerve.

the widening of the arterial curve suggests that the tumour had grown into the anterior depth of its concavity. It may be that such a forward extension of the tumour is necessary if a central scotoma is to be produced, whether or not obstruction of the ophthalmic artery be an intermediary factor. In two patients with moderate temporal extensions of pituitary adenomata the tumour passed under the posterior portion of the optic nerve and the maximum elevation of the internal carotid artery was at its bifurcation. In neither case was there any scotomatous change.

A widening of the carotid curve was demonstrated both by arteriography and operation in another patient with a left lateral protrusion of a pituitary adenoma, but as the left eye was blind it was impossible to state whether or not there had been an early central scotoma.

In the following case a central scotoma was associated with a swelling which raised and stretched the optic nerve just behind the optic foramen. The position of the internal carotid artery had not been recorded.

Case 4.—A man aged 32 years was admitted to the Richmond Hospital on April 27, 1937. Four years previously he had noticed that the vision of the left eye was poor and that he could not see objects if he looked directly at them. Headaches had also begun four years previously. At first they were not severe but they became worse and on admission to hospital they were constant and incapacitating. He had had occasional attacks of "weakness" for the past year. General neurological examination was negative. A radiograph of the skull showed destruction of the left anterior clinoid process with erosion of the sphenoidal ridge beside it. The left optic foramen appeared a little larger than the right.

May 2, 1937.—Ophthalmic examination showed visual acuity to be: right, 6/5 (Snellen); left, counted fingers at 1 metre. The right eye showed œdema of the nasal margin of the disc. The left had a pale disc with clear margins and normal vessels.

The visual field of the right eye showed an enlarged blind spot but was otherwise normal. In the left eye there was a large cæco-central scotoma for 3/330, 1/330 white, with some general depression (Fig. 22). The diagnosis was made of a lesion, probably meningioma or aneurysm in the region of the left optic foramen.

Ventriculography was performed on May 20. A few drops of fluid escaped from the right ventricle under pressure, but no more could be obtained: 20 c.cm. were removed from the left ventricle and replaced by air. The films showed the anterior part of the left ventricle to be displaced from the mid-line. There was no air in the right ventricle or in the third ventricle. At operation a right transfrontal exposure was made. A very large subarachnoid cyst had practically replaced that part of the right frontal lobe which lay in front of the pre-central sulcus. On the floor of the cyst appeared the chiasma and both optic nerves. The left optic nerve was stretched tightly over another swelling about the size of a pea (Fig. 18). There was a suggestion of pulsation in the swelling which was therefore taken to be an aneurysm. A blunt hook was passed along the nerve under the falciform fold and the ligament divided as far forward as the bone. The latter seemed to have been eroded. This manœuvre released the anterior part of the nerve so that its upward convexity was not so acute. The operation relieved the headaches but did not improve vision.

Nov. 14, 1947.—The field of the right eye was unchanged. The left eye had scotoma for 1/330, breaking through, but otherwise no change (Fig. 23).

In the cases just recorded pressure on the optic nerve or on the internal carotid artery was exerted primarily by the growth of a tumour below these structures. In the following case the pressure was exerted from above.

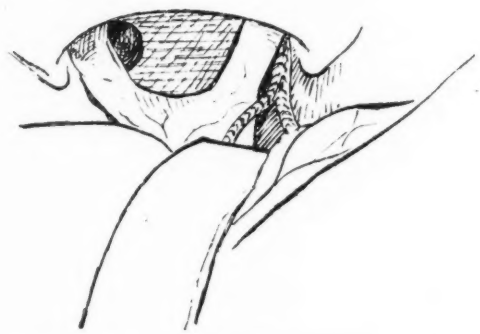

FIG. 18.—Case 4. Presumed aneurysm under the left optic nerve.

Case 5.—A woman aged 37 years was admitted to the Richmond Hospital on Jan. 15, 1948. Eight months before admission she began to suffer from severe morning headaches. The severity of these headaches had somewhat diminished before her arrival in hospital, but as they declined the patient became euphoric, expansive, and jocular with little appreciation of her illness. Vision began to fail three months before admission. On examination there was complete anosmia but apart from the visual defects no other neurological sign. Ophthalmic examination showed visual acuity to be: right, 6/24 (Snellen); left, hand movements only. The right disc showed papillœdema of less than 1 diopter; the left disc was pale with clear margins and normal vessels.

The visual field of the right eye showed a temporal hemianopic defect for 3/330 and 1/330 white, with small macular loss for 2/2000 white, and of the left eye a large central scotoma for hand movements (Fig. 24).

Jan. 26, 1948.—Ventriculography showed displacement of the anterior portions of both ventricles to the left side. At operation a large meningioma was found covering most of the right orbital roof and cribriform

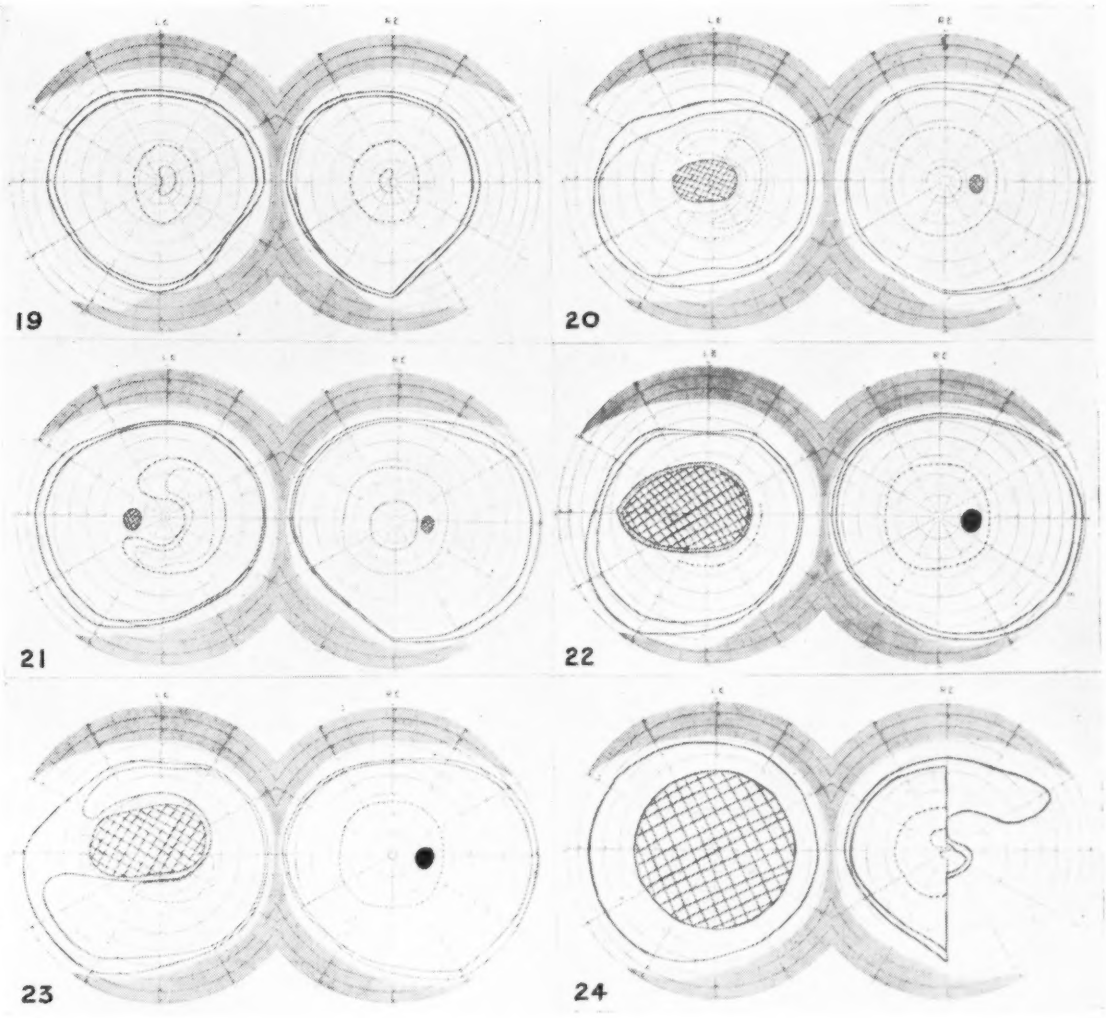

FIG. 19.—Case 2. Visual acuity: both eyes, 6/36. Objects: 3/330, 1/330, 2/2000 (white), 10/2000 (red).

FIG. 20.—Case 3. Visual acuity: right eye, 6/5; left, counts fingers at 1 metre. Objects: 3/330, 1/330, 2/2000, 5/2000 (white), right eye, 5/2000 (red).

FIG. 21.—Case 3. Visual acuity: right eye, 6/5; left, 3/60. Objects: 3/330, 1/330, 5/2000, 2/2000 (white), right eye, 5/2000 (red).

FIG. 22.—Case 4. Visual acuity: right eye, 6/6; left, counts fingers at 1 metre. Objects; 3/330, 1/330, 2/2000.

FIG. 23.—Case 4. Visual acuity: right eye, 6/6; left, counts fingers at 1 metre. Objects: 3/330, 1/330, 2/2000 (white), right eye, 10/2000 (red).

FIG. 24.—Case 5. Visual acuity: right eye, 6/24; left, hand movements. Objects: 3/330, 1/330, 2/2000.

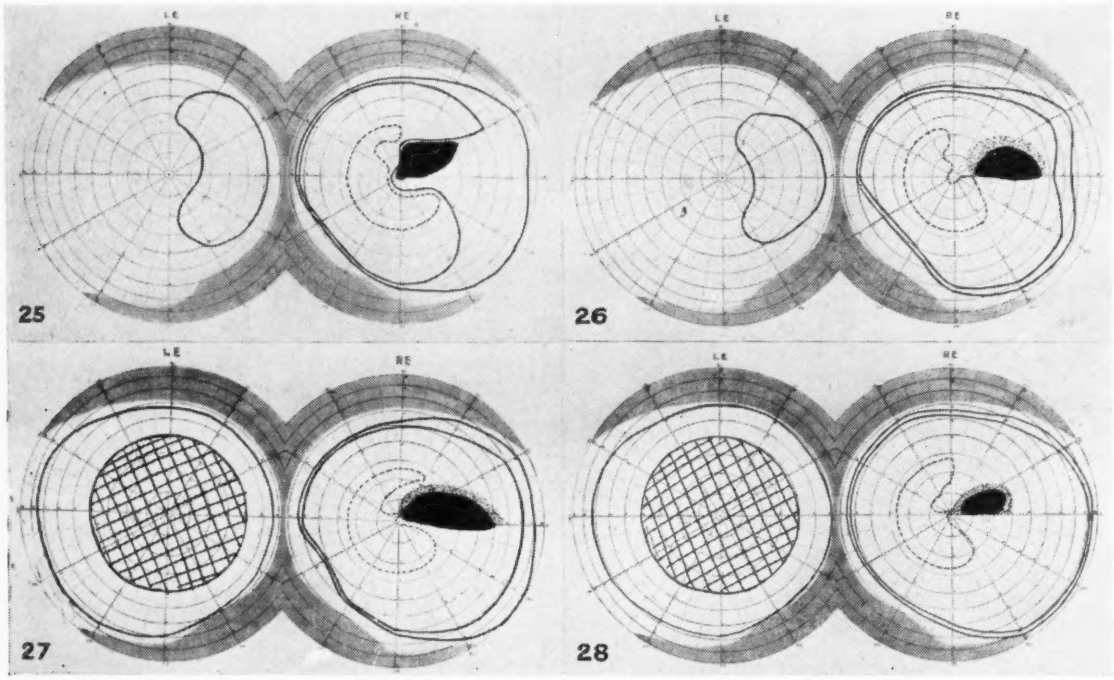

FIG. 25.—Case 5. Visual acuity: right eye, 6/24; left, counts fingers at 1 metre. Objects: 3/330, 1/330, 2/2000.

FIG. 26.—Case 5. Visual acuity: right eye, 6/24; left, counts fingers at 1 metre. Objects: 3/330, 1/330 2/2000.

FIG. 27.—Case 5. Visual acuity: right eye, 6/18; left, hand movements. Objects: 3/330, 1/330, 2/2000.

FIG. 28.—Case 5. Visual acuity: right eye, 6/18; left, hand movements. Objects: 3/330, 1/330, 2/2000.

plate. It extended backwards over both optic nerves and across to the left side of the anterior cranial fossa. The tumour was completely removed on the right side but some of its extension to the other side was left in situ. Postoperative charts showed a steady recovery in the peripheral field of the right eye with shrinkage of the residual scotoma. There was no material change in the field of the left eye. (Feb. 15, 1948: Fig. 25. Mar. 14, 1948: Fig. 26. May 2, 1948: Fig. 27. July 7, 1948: Fig. 28.).

Comment.—It is impossible to say to what extent the tumour had depressed the right optic nerve or had involved the ophthalmic artery. The case is included because of the association of a central scotoma with a tumour affecting the optic nerve close to the optic foramen.

In four of the five cases just recorded the lesions and their relations to the optic nerve were verified at operation; in Case 1 there was sufficient evidence to support the diagnosis of a pituitary adenoma with a temporal extension. In the following case the optic nerve was not seen but the evidence suggests that pressure had been exerted on its upper surface.

Case 6.—A man aged 38 years in 1925 had sustained concussion and a scalp wound in the right parietal region. He recovered rapidly and resumed work in ten days. In 1936 he began to have attacks of "unconsciousness" lasting about fifteen minutes and occurring about twice a year. A detailed description of these attacks could not be obtained. In the last week of February 1939 he began to notice some transient blurring of vision. On examination on March 3 the visual acuity was 6/6 (Snellen) in each eye. The right disc was normal; the upper margin of the left disc was very slightly blurred. There was no gross defect in either visual field. One week later there was slight œdema of the upper margin of the right disc, while the left disc was unchanged.

The patient was admitted to the Richmond Hospital on July 19, 1939. General neurological examination was negative, and the skull appeared normal radiographically. At ophthalmic examination on Aug. 2, 1939, visual acuity of each eye was 6/6 (Snellen). The right disc had papillœdema of 2 diopters; the left had blurring of upper margin. There was paresis of the left inferior rectus muscle. With the exception of enlarged blind spots, especially the right, the visual fields were normal. On Aug. 27 visual acuity of the

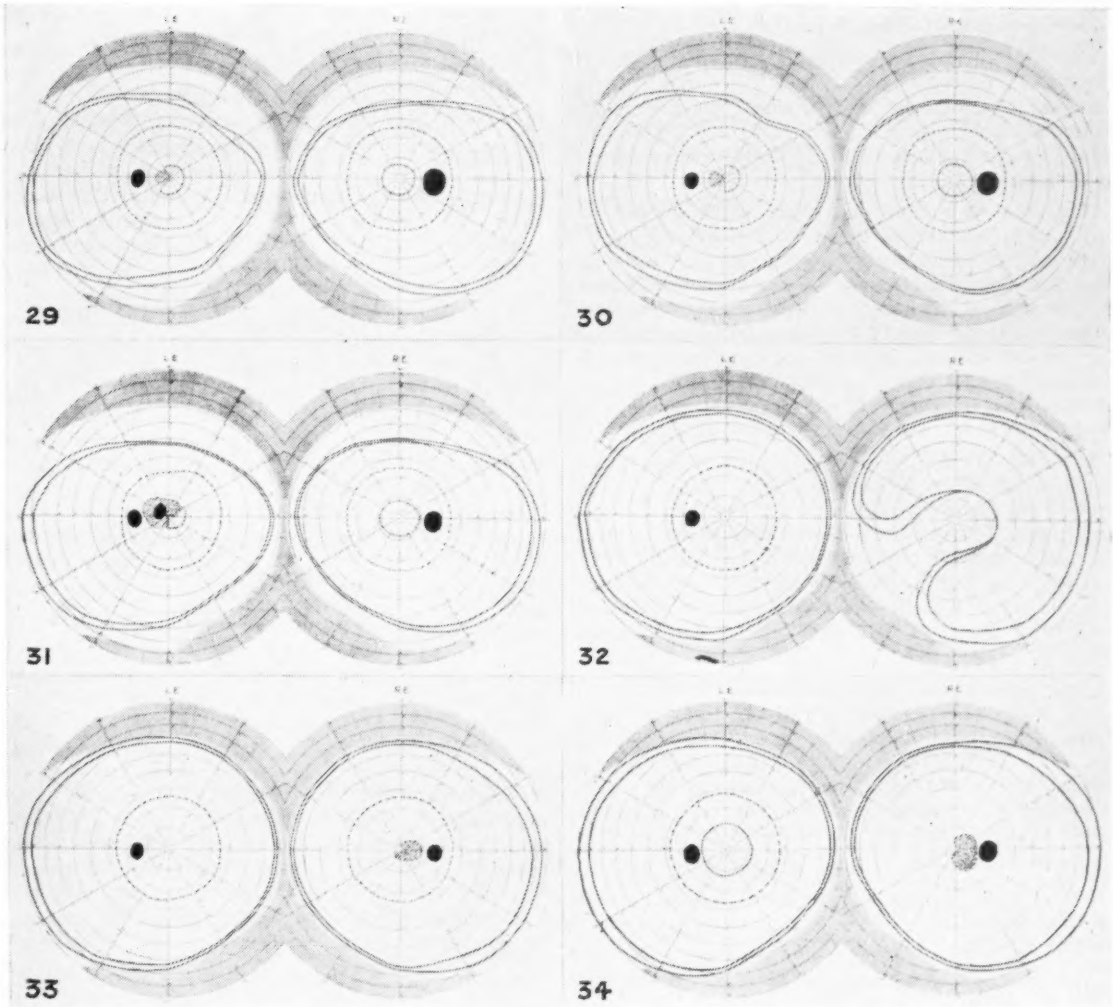

FIG. 29.—Case 6. Visual acuity : right eye, 6/6 ; left, 6/12. Objects : 3/330, 1/330, 2/2000 (white), 5/2000 (red).

FIG. 30.—Case 6. Visual acuity : both eyes, 6/6. Objects : 3/330, 1/330, 2/2000 (white), 5/2000 (red).

FIG. 31.—Case 6. Visual acuity : both eyes, 6/6. Objects : 3/330, 1/330, 2/2000 (white), 5/2000 (red). Scotoma : 2/2000, 5/2000, 10/2000 (white).

FIG. 32.—Case 7. Visual acuity : right eye, 3/60, left, 6/6. Objects : 3/330, 1/330, 2/2000.

FIG. 33.—Case 7. Visual acuity : right eye, 6/9 ; left, 6/5. Objects : 3/330, 1/330, 2/2000.

FIG. 34.—Case 7. Visual acuity : right eye, 6/6 ; left, 6/5. Objects : 3/330, 1/330, 2/2000 (white), 5/2000 (red). Scotoma : 2/2000, 5/2000 (white).

right eye was 6/6 and of the left 6/12 (Snellen). Papilloedema of the right disc had increased to 3½ diopters, while the slight blurring of the upper margin of the left disc remained unchanged. Both the left inferior rectus muscle and the left external rectus were weak.

Aug. 27.—Perimetric examination showed enlarged blind spots, especially on the right. The left eye had paracentral scotoma for 2/2000, white, and a temporal sector defect involving fixation point for 5/2000, red (Fig. 29). General neurological examination continued to be negative.

Aug. 29.—An opening was made in the left parietal region just above the lambdoid suture for ventriculography. The bone was very vascular and the ventricular needle met with a hard tumour mass just below the cortex. At this moment the patient said that his right arm was numb, and it was noticed that his mouth was drawn to the left side and that he could not raise his left eyelid. At operation a large bone flap was turned down and the tumour, which proved to be a parasaggital meningioma (5½ by 4 by 4 cm.), was completely removed.

Sept. 17.—At the ophthalmic examination the visual acuity of both eyes was 6/6 (Snellen). The right disc showed papilloedema of 3 diopters. The left disc was unchanged. The muscles of the eyes were normal. Perimetry showed enlargement of the blind spots, especially the right. The left eye had a paracentral scotoma for 2/2000, white, and temporal hemianopic defect with sparing of the fixation point for 5/2000, red (Fig. 30).

Dec. 10.—Ophthalmic examination showed visual acuity of both eyes to be 6/6 (Snellen). The right disc showed slight blurring of the upper margin. The left disc showed very slight pallor. Perimetry showed enlargement of the blind spots, especially the right. In the left eye paracentral scotoma was more intense as shown for 5/2000 and 10/2000, white (Fig. 31).

March 3, 1940.—Visual fields were normal.

Dec. 1948.—The patient has been well except for an occasional attack of slight tingling in the right arm : consciousness was not lost in these attacks.

Comment.—The paracentral scotoma in the left eye did not show hemianopic characteristics. The presence of this scotoma, together with a disc which was within normal limits in the left eye and papilloedema in the right, led us to expect a left-sided baso-frontal tumour. If ventriculography had not been attempted this would have led to a left-frontal exposure. It would appear in retrospect that the swelling or downward displacement of the left hemisphere in this patient had exerted pressure on the left optic nerve and possibly on the ophthalmic artery under the nerve. Involvement of the third cranial nerve was probably due to a cerebral herniation through the anterior part of the tentorial opening, or into the pituitary fossa. We have noted on other occasions herniation of the posterior end of the gyrus rectus over the sharp dural fold which continues the edge of the tentorium to the anterior clinoid process. Vincent and others (1938) reported two cases of primary optic atrophy associated with meningiomas, one parieto-occipital and one parasaggital in the parietal region. Beck (1947) published a case of the same nature.

Although the following case was not verified by operation the diagnosis of an aneurysm close to the optic foramen seems to be justified.

Case 7.—A man aged 49 years was admitted to the Richmond Hospital on July 5, 1947. In June 1944 he had begun to suffer from headaches which were intermittent at first but gradually became continuous. They affected chiefly the right frontal and temporal regions and appeared to have a neuralgic character. On Oct. 27, 1944, he noticed double vision for the first time, and examination on Nov. 1 revealed paralysis of the right external rectus muscle. Visual acuity was : right eye, 6/5 ; left eye, 6/5 (Snellen). There was retinal arteriosclerosis. Discs and corneal sensation were normal. There was no intracranial bruit. Neurological examination was negative except for the sixth nerve palsy. Blood pressure was 180/110 mm. Hg. Neither general medical nor radiographic examination revealed any abnormality, and the optic foramina were normal in appearance. Compression of the right common carotid artery was found to relieve the pain in the right temporal and frontal regions.

Nov. 15.—A partial paralysis of the right third nerve was discovered in addition to that of the sixth nerve already noted. There was subjective anæsthesia of the right frontal region and a definite lowering of corneal sensation on that side. Ophthalmic examination revealed that the visual acuity of the right eye had diminished to counting fingers at 1 metre. A large central scotoma breaking through downwards and inwards was revealed by confrontation test. Vision of the left eye remained at 6/5 (Snellen). Arteriography was suggested, but the patient preferred to await developments.

Feb. 21, 1945.—At the ophthalmic examination the right eye had partial third nerve palsy ; the pupil was slightly dilated and reacted sluggishly to direct illumination ; the disc was somewhat pale with clear margins : visual acuity 3/60, and central scotoma breaking through downwards and inwards. The left eye was normal (Fig. 32).

April 14, 1946.—At ophthalmic examination the third nerve palsy had completely disappeared and corneal sensation was normal. Visual acuity of right eye was 6/9 (Snellen), and the visual field showed a scotoma involving the cæco-central region but sparing the macula (Fig. 33).

The patient was able to continue his work until July 1947, when he returned because the headaches had increased in severity. On this occasion the right disc was pale with clear margins, and connective tissue on the surface and the left disc showed papilloedema of two

diopters. The latter finding was attributed to hypertension associated with the arteriosclerosis.

July 9, 1947.—The right common carotid artery was injected with perabrodil. The arteriogram did not demonstrate a characteristic aneurysmal sac, but it showed widening and irregularity of the carotid shadow at the last bend of the vessel. The picture suggested an aneurysm lying both inside and outside the cavernous sinus. The common carotid artery was partly occluded in the neck. This procedure relieved the headache to some extent. Six days later the artery was completely occluded. Headache was severe for two days and then gradually disappeared.

June 20, 1948.—The patient appeared well in every way. Visual acuity was : right, 6/6 (Snellen) ; left, 6/6 (Snellen). In the right eye there was an enlarged blind spot and a temporal paracentral scotoma partly encircling but not involving the fixation point (Fig. 34).

The right disc was pale with clear margins and connective tissue on the surface. The left showed slight œdema of the margins. In both retinæ the arteriosclerotic appearances had become more marked. The blood pressure at this time was 205/140 mm. Hg.

Comment.—The history of this patient suggests that he had an aneurysm inside the cavernous sinus and that it extended sufficiently upwards to implicate the right optic nerve. Presumably thrombosis occurred and a spontaneous cure was the result. Ligature of the carotid artery was probably unnecessary though justified by the arteriogram.

Saccular aneurysms of the internal carotid artery inside the anterior part of the cavernous sinus do not appear to interfere with the optic nerve or its blood supply so long as they remain strictly intracavernous. Jefferson (1938) reported seven such cases in each of which vision was unimpaired.

Discussion

Ophthalmologists have shown an increasing tendency to attribute visual defects to interference with the blood supply rather than to direct pressure on the nerve fibres. It is difficult however to envisage a lesion which would press sufficiently on the blood vessels on the surface of the optic nerve without at the same time pressing on the nerve fibres. On the other hand any effective pressure on the nerve must affect the vessels. The possibility of obstruction to the vessels *before* they reach the nerve is examined in this paper.

There appears to be general agreement that the tumour which raises or depresses the optic nerve close to the optic foramen is particularly liable to be associated with a central scotoma. It has been pointed out above that a tumour in this situation which either presses the optic nerve downwards or pushes the internal carotid artery upwards might kink or obstruct the ophthalmic artery or its intracranial branches. In this way the blood supply of a segment of the macular bundle might be impaired. The blood supply of the intracranial and intracanalicular portions of the bundle is said to be poor when compared with that of the rest of the optic nerve, and this relative poverty has been evoked to explain the alleged vulnerability of the macular fibres.

The hypothesis of hypersensitivity to pressure of the papillo-macular bundle fails to explain why demonstrable pressure on the nerve should in one case produce a purely peripheral defect and in another a defect of a purely central type, nor does it explain why the site and direction of pressure seem to be significant.

On the hypothesis of vascular obstruction the presence or absence of a central scotoma would depend on whether or not a particular vessel or group of vessels were involved. An obstruction to blood vessels has not been demonstrated at operation nor has it been shown by arteriography. As the shadow of the ophthalmic artery fails to appear in many good arteriograms its absence cannot be taken to imply obstruction to that vessel. When the internal carotid artery is occluded proximal to its ophthalmic branch the effect on vision varies with the nature of the occlusion. In spontaneous closure due to thrombosis vision in the corresponding eye is lost, whereas surgical ligation leaves vision unaffected (Walsh and King, 1942). The ophthalmic artery itself has been ligatured in cases of carotid-cavernous aneurysm without producing any visual defects. No opinion can be offered on the effect of partial obstruction to the ophthalmic artery. Lillie and Adson (1934) reported two cases of callus formation in the optic canal associated with a central scotoma. It is probable that whatever the pressure on the nerve itself in these cases, there was some interference with the blood flow through the vessel or through the branches arising in the canal.

Although the presence of a central scotoma directs attention to the optic nerve close to the optic foramen, exploration may not reveal any lesion in this situation. Some years ago McConnell and Mooney (1938) reported a case of subchiasmal aneurysm associated with a definite central scotoma in the right visual field and one for small red objects only in the left. At operation the optic nerves and the chiasma appeared normal in every respect. In this case some factor other than direct pressure must have been concerned in the production of the central scotoma.

Appearances at operation in the majority of cases cannot but suggest that the obvious pressure on the nerve is related to the scotomatous defect,

but our observations and some of those recorded in the literature suggest that the problem is of a more complex nature.

Summary

Current theories on the causation of central scotomata associated with space-occupying intracranial lesions are reviewed. The possibility of pressure on the intracranial portion of the ophthalmic artery as a factor in the production of scotomata is discussed.

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THE TONIC PUPIL

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The peculiar phenomenon of the tonic pupil was first described in detail by Strasburger in 1902. Later in the same year both Saenger and Nonne reported further cases and Saenger proposed the name " myotonic pupillary movement " for the condition. Until this time the disorder had not been separated from others causing mydriasis or alteration in the pupillary reflexes. Yet the curious slowness of pupillary movement, characteristic of the condition, must have been recognized earlier ; indeed in 1818 James Ware described a patient who very probably had a tonic pupil. His patient, whose pupillary abnormality had been known to exist for at least twenty years, was " a lady between twenty and thirty years of age, the pupil of whose right eye, when she is not engaged in reading or in working with her needle, is always dilated very nearly to the rim of the cornea ; but whenever she looks at a small object, nine inches from the eye, it contracts within less than a minute to a size nearly as small as the head of a pin . . . its contraction never remains long after the attention is withdrawn from a near object."

After 1902 the condition was reported on several occasions, both in this country (Markus, 1906 ; Weber, 1923 ; Moore, 1923, 1931 ; and Morgan and Symonds 1927, 1931) and abroad, but it did not attract much attention until the work of Holmes (1931) and Adie (1931, 1932). To Adie in particular must be given the credit for attempting a synthesis of available information into a semeiological plan. He divided the tonic pupil into two forms, the typical and the atypical, each of which might be associated with absence of one or more tendon reflexes, but with no other neurological abnormality. Collier (1933) first called this combination " Adie's Syndrome," a name which has been generally applied in Europe and America. In this country, following Bramwell's (1936) suggestion, the double eponymous title of the " Holmes-Adie syndrome " has been perhaps more widely used.

The " typical " tonic pupil, in Adie's view, was a unilateral disorder in which the affected pupil was larger than normal, did not react to torch light but dilated slowly in the dark, subsequently contracting slowly in daylight, and showed a characteristically slow contraction and relaxation with ocular convergence. The " atypical " forms were less clearly defined but included some forms of internal ophthalmoplegia and complete light rigidity with a tonic convergence reaction. Since Adie's description, this conception of the atypical tonic pupil has been so far enlarged upon that, for example, Lowenstein and Friedman (1942) write, " In atypical cases all the modifications observable in pupillary disease both of syphilitic and other causation may be exhibited." Similarly Alajouanine and Morax (1938) claim that between the typical tonic pupil and the Argyll Robertson pupil all intermediary forms are possible. If these statements are even partly true the practical difficulties of diagnosis which not infrequently arise are understandable enough.

Apart from what distinctive pupillary abnormalities must necessarily be found before a diagnosis can be made, two other problems remain to be solved : (1) the site of the anatomical lesion and (2) the nature and specificity, or otherwise, of the underlying pathological process. This paper is an attempt to throw light on some of these problems.

Clinical Observations

Fifteen patients, twelve females and three males, varying in age from 12 to 55 years, have been studied, in each of whom was found evidence of " tonicity " of one or more of the three principal actions of the intrinsic ocular muscles, viz : pupillary contraction on exposure to light and with ocular convergence, and the ciliary muscle response to accommodation. The detailed clinical findings in these patients are set out in Tables I and II.

Symptoms.—Of the fifteen patients, eleven were originally seen because of pupillary inequality noticed either by themselves, their friends, or their doctors ; and four attended because of blurring of vision with or without headaches.

TABLE I

UNILATERAL CASES

Case No.	Sex	Age (yrs.)	Presenting symptoms	Pupil size (mm.)	Pupil shape	Light reflex	Convergence reaction	Delay in accommodation	1% Homatropine	¼% Eserine	2½% Amechol	Absent tendon reflexes	Other findings
1	F	41	1945 : (*a*) transient blurring of vision ; (*b*) enlargement of R. pupil	R. 5	Irregularly oval, eccentrically placed.	T.L. nil E.L. 5→2·5 mm. in 5 secs. 2·5→5 mm. in 10 secs.	5→3·5 mm. in 10 secs. 3·5→5 mm. in 20 secs.	N→F 3 secs. F→N 6 secs.	5→8 mm. in 30 mins.	8→6 mm. in 40 mins.	4·5 → 3·5 mm. in 30 mins.	R. and L. T.J.s A.J.s	W.R. (blood) negative
				L. 3·5	Circular	T.L. and E.L. normal	Normal.	No delay	3·5 → 8 mm. in 30 mins.	8 → 3·5 mm. in 40 mins.	No change in 30 mins.	R. K.J.	
2	F	12	1946 : facial habit spasm ; pupil changes discovered on routine examination	R 6	Slightly irregular ; inferior nasal margin flattened	T.L. nil E.L. 6→4 mm. in 6 secs. 4→6 mm. in 4 secs.	6→4 mm. in 10 secs. 4→6 mm. in 15 secs.	No delay	—	—	6·5 → 5·5 mm. in 30 mins.	All reflexes absent	W.R. (blood) negative
				L. 7·5	Circular	T.L. and E.L. normal	Normal	No delay	—	—	No change in 30 mins.		
3	F	48	1941 : endogenous depression ; pupil changes known to exist for more than 20 yrs.	R. 3	Circular	T.L. and E.L. normal	Normal	No delay	3→8 mm. in 30 mins.	8 → 3·5 mm. in 30 mins.	No change in 30 mins.	All reflexes present	W.R. (blood and CSF) negative. CSF examination normal
				L. 3·5	Irregularly oval ; angulated at 2 o'clock ; inferior nasal margin flattened	T.L. nil E.L. slow contraction to 2·5 mm. ; slower relaxation	3·5→1·5 mm. in 15 secs. 1·5→3·5 mm. in 15 secs.	No delay	3·5 → 6 mm. in 30 mins.	6 → 3·5 mm. in 30 mins.	No change in 30 mins.		
4	F	48	1945 : (*a*) pain over L. eye ; (*b*) transient blurring of near vision L. eye	R. 5	Circular	T.L. and E.L. normal	Normal	No delay	5→7 mm. in 30 mins.	7→4 mm. in 30 mins.	No change in 30 mins.	R. and L. T.J.s A.J.s	W.R. (blood and CSF) negative. CSF examination normal
				L. 3·5	Slightly irregular ; upper nasal margin flattened	T.L. nil E.L. 5→3 mm. slowly 3→5 mm. very slowly	3·5 mm.→3 mm. in 5 secs. 3 mm.→3·5 mm. in 10 secs.	N→F 4 secs. F→N 2 secs.	4 → 6·5 mm. in 30 mins.	6·5 → 4·5 mm. in 30 mins.	No change in 30 mins.		
5	F	24	1945 : epilepsy (idiopathic) ; pupil changes discovered on routine examination	R 5	Circular	T.L. and E.L. normal	Normal	No delay	—	—	No change in 30 mins.	R. K.J. A.J.	W.R. (blood and CSF) negative. CSF examination normal
				L. 6	Slightly irregular, eccentrically placed	T.L. nil E.L. 6→4 mm. in 15 secs. 4→6 mm. in 35 secs.	6→4 mm. in 15 secs. 4→6 mm. in 40 secs.	N → F none F → N 2 secs.	—	—	Sluggish No change in 30 mins.	L. K.J. and A.J.	

6	F	42	1947 : (*a*) sudden enlargement L. pupil ; (*b*) aching pain L. eye	R. 3 L. 5·5	Circular Irregular, eccentrically placed	T.L. and E.L. normal T.L. and E.L. nil. No dilatation in the dark	Normal No contraction	No delay N → F none F→N 5·5 secs. Near point: R.19mm. L. 29mm.	3·5 → 6 mm. in 30 mins. 5·5 → 7·5 mm. in 30 mins.	7 → 2·5 mm. in 20 mins. 8→3 mm. in 20 mins.	No change in 30 mins. 5·5→4 mm. in 30 mins. (After 30 mins. delayed accommodation reduced to 2 secs.)	R. A.J. diminished	W.R. (blood) negative
7	F	34	1946 : (*a*) pupil irregularity noticed by friends; (*b*) headaches, locally over R. eye and more generalized. (*c*) aching pains in all limbs especially in the mornings on waking	R. 6 L. 4·5	Irregular, eccentrically placed Circular	T.L. nil E.L. 7→4·5 mm. in 30 secs. 4·5→7 mm. in 15 secs. T.L. and E.L. normal	6→4 mm. in 10 secs. 4→6 mm. in 30 secs. Normal	N→F 1 sec. F→N 3 secs. No delay	— —	— —	6→4 mm. in 30 mins. No change in 30 mins.	R. A.J. Sluggish R. K.J. and arm reflexes	W.R. (blood) negative
8	M	30	1947 : closed head injury. R. occipital bone. Sequelae: (*a*) bilateral anosmia; (*b*) blurring of near vision L. eye (no diplopia or ptosis)	R. 4·5 L. 7	Circular Slightly irregular	T.L. and E.L. normal T.L. nil E.L. 7→5 mm. slowly 5→7 mm. very slowly	Normal 7→4 mm. in 3 secs. 4→7 mm. in 20 secs.	No delay N→F no delay F → N 5 secs.	— —	4·5 → 2 mm. in 30 mins. 7→2 mm. in 30 mins.	No change in 30 mins. 7→5 mm. in 30 mins.	All reflexes present	W.R. (blood) negative

T.L. = torch light.
E.L. = electric light.
N⇄F = uniocular gaze shifted from near ⇄ far object.
S.J., T.J., A.J., K.J. = supinator, triceps, ankle, and knee jerk.

TABLE II

BILATERAL CASES

Case No.	Sex	Age (yrs.)	Presenting symptoms	Pupil size (mm.)	Pupil shape	Light reflex	Convergence reaction	Delay in accommodation	1% Homatropine	¼% Eserine	2½% Amechol	Absent tendon reflexes	Other findings
9	M.	40	1941 : intermittent pains in hips, knees, wrists, and fingers (no arthritis demonstrable clinically or radiologically ; pupillary inequality first noticed 20 years ago	R. 5	Oval, axis ↗	T.L. nil E.L. 5→3·5 mm. in 15 secs. 3·5→5 mm. in 10 secs.	5→3·5 mm. in 20 secs. 3·5→5 mm. in 25 secs.	N→F no delay F→N 3 secs.	5→7 mm. in 1 hour	—	5→3·5 mm. in 30 mins.	All absent except R. and L. B.J.s	W.R. (blood and CSF) negative. CSF examination normal
				L. 4	Slightly irregular ; temporal margin flattened	T.L. nil E.L. 4→2·5 mm. in 15 secs. 2·5→4 mm. in 10 secs.	4→2·5 mm. in 20 secs. 2·5→4 mm. in 25 secs.	N→F no delay F→N 4 secs.	4→8 mm. in 1 hour	—	4→3 mm. in 30 mins.		
10	F.	49	1945 : (*a*) transient blurring of near vision R. and L. ; (*b*) pupillary inequality noticed by friends	R. 2·5	Irregular, upper temporal margin flattened	T.L. nil E.L. 3·5→2·5 mm. in 7 secs. 2·5→3·5 mm. in 5 secs.	2·5→2 mm. in 5 secs. 2→2·5 mm. in 5 secs.	N→F no delay F→N 2 secs.	2·5→6 mm. in 40 mins.	6→3 mm. in 35 mins.	No change after 30 mins.	All reflexes absent	W.R. (blood and CSF) negative. CSF examination normal
				L. 3·5	Irregular, lower nasal margin flattened	T.L. nil E.L. 4→2·5 mm. in 3 secs. 2·5→4 mm. in 20 secs.	3·5→2·5 mm. in 20 secs. 2·5→3·5 mm. in 40 secs.	N→F no delay F→N 4·5 secs.	3·5→6 mm. in 40 mins.	6 → 1·5 mm. in 35 mins.	No change after 30 mins.		
11	M.	48	1937 : pupillary inequality noticed ; no ocular symptoms	R. 4	Irregular and eccentrically placed	T.L. nil E.L. 4→2 mm. in 5 secs. 2→4 mm. in 30 secs.	4→3 mm. in 90 secs. 3→4 mm. in 135 secs.	N→F 1 sec. F→N 4 secs.	3·5 → 7 mm. in 20 mins.	—	No change after 30 mins.	R. and L. A.J.s R. and L. T.J.s R. S.J.	W.R. (blood) negative
				L. 7	Irregular and eccentrically placed	T.L. nil E.L. 7→2 mm. in 5 secs. 2→7 mm. in 30 secs.	7→4·5 mm. in 90 secs. 4·5→7 mm. in 135 secs.	N→F no delay F→N 1 sec.	7 → 7·5 mm. in 10 mins.	—	6→5·5 mm. in 30 mins.		
12	F.	12	May, 1947 : L. pupil enlarged (tonic pupil diagnosed) ; March, 1948 : both pupils enlarged ; no ocular symptoms	R. 9	Almost circular but eccentrically placed in the iris	T.L. nil E.L. 9→8 mm. slowly 8→9 mm. very slowly	9→7 mm. in 15 secs. 7→9 mm. in 30 secs.	N→F no delay F→N 2 secs. (near point, 10 cm.)	—	9→2 mm. in 30 mins.	9→3·5 mm. in 30 mins. (delayed accommodation abolished : near point, 5 cm.)	R. and L. A.J. R. T.J. S.J.	W.R. (blood and CSF) negative. CSF examination normal. Crying →slow contraction and subsequent slow relaxation of both pupils
				L. 9	As R.	T.L. nil E.L. nil	9→6 mm. in 60 secs. 6→9 mm. in 90 secs.	N→F no delay F→N no delay (near point, 12 cm.)	—	9→2 mm. in 30 mins.	9→2 mm. in 30 mins. (near point, 6 cm.)		

13	F.	44	1941 : (*a*) transient blurring of near vision L. > R. (*b*) R. pupil < L.	R. 3	Very irregular	T.L. nil E.L. 3→2·5 slowly 2·5→3 very slowly	3→1·5 mm. in 3 secs. 1·5→3 mm. in 5 secs.	N→F 3 secs. F→N no delay	3→7 mm. in 30 mins.	7 → 1·5 mm. in 30 mins.	No change after 30 mins.	R.A.J. sluggish	W.R. (blood) negative
				L. 5	Very irregular	T.L. nil E.L. nil	5→3 mm. in 10 secs. 3→5 mm. in 10 secs.	N→F no delay F→N 5·5 secs.	5→7 mm. in 30 mins.	7 → 3·5 mm. in 30 mins.	No change after 30 mins.		
14	F.	42	(*a*) Recurrent non-specific headaches for 20 years. (*b*) 1945 : transient blurring of vision L. eye	R. 3·5	Slightly irregular	T.L. normal E.L. normal	3·5 → 2·5 mm. promptly 2·5→3·5 mm. in 4 secs.	N→F no delay F→N 2 secs.	3·5 → 9 mm. in 30 mins.	9 → 2·5 mm. in 30 mins.	No change after 30 mins.	R. and L. A.J.s	W.R. (blood and CSF) negative. CSF examination normal
				L. 5·5	Slightly irregular	T.L. nil E.L. nil	5·5→4 mm. in 10 secs. 4→5·5 mm. in 15 secs.	N→F no delay F→N 5 secs.	5·5 → 7·5 mm. in 30 mins.	7·5 → 2·5 mm. in 30 mins.	5·5→5 mm. in 30 mins.	—	
15	F.	55	(*a*) Intermittent aching pain in all limbs for 30 years. (*b*) Lacinating pain in the legs, single stabs occurring repeatedly daily for 10 years ; (*c*) precordial angina-like pains occurring at rest and with exertion, 2 years ; (*d*) pupillary irregularity noticed for 11 years	R. 2	Irregular, eccentric ; displaced upwards and inwards	T.L. nil E.L. nil No dilatation in the dark	2→1·5 mm. in 10 secs. 1·5→2 mm. in 15 secs.	No delay	2 → 4·5 mm. in 40 mins.	—	2·5→1 mm. in 30 mins.	All reflexes absent	W.R. (blood and CSF) negative. CSF examination, proteins 50 mg. per 100 ml., otherwise normal. No clinical, radiological, or electrocardiographic evidence of cardiac disease over an observed period of 12 years
				L. 3·5	Irregular, eccentric ; displaced upwards and inwards	T.L. prompt flicker of contraction E.L. normal contraction (3·5→3) and relaxation	3·5→2 mm. in 15 secs. 2→3·5 mm. in 45 secs.	No delay	3·5 → 6 mm. in 40 mins.	—	3→2 mm. in 30 mins.		

T.L. = torch light.
E.L. = electric light.
N⇌F = uniocular gaze shifted from near ⇌far object.
S.J., T.J., A.J., K.J. = supinator, triceps, ankle, and knee jerk.

Pupillary Abnormalities.—In eight cases there was evidence of unilateral pupillary disorder only, in seven cases bilateral changes were found—a total of twenty-two affected pupils. The proportion of bilateral cases is much higher than in other recorded series.

Size and Shape.—All the patients were examined in dull diffuse daylight and the pupillary size was noted after fixation on a distant object, allowing sufficient time for the pupil to reach a constant size. Measurement is sometimes difficult where pronounced irregularity exists—in general the diameter of the circle which most closely approximated in area to that of the pupil was chosen. Among the twenty-two affected eyes the pupil diameter varied from 2 mm. (Case 15) to 9 mm. (Case 12). In the eight unilateral cases the affected pupil was larger than the normal one in seven and smaller in one case. In the seven bilateral cases a diameter of 3·5 mm. or less was seen in five eyes, this being less than the minimum normal diameter observed under these conditions of illumination. It is apparent, therefore, that a tonic pupil may be of any size, even miotic, although it is more commonly larger than a normal one in daylight.

The shape of the pupil has received little attention, though it is probably of considerable importance in considering the site of the lesion. In all cases it was irregular; some pupils were only slightly deformed, others markedly so. Sectors of the margin may be straight or angulated; others appear to be retracted towards the attached border of the iris, giving an ovoid shape to the pupil. In some eyes the pupils appeared to be made up of two halves—both semicircular but of different sizes. These irregularities of the iris margin are usually retained when the pupil contracts. Moreover, the pupil may be eccentrically placed in the iris; this was noted in eight of the twenty-two affected eyes. Partly this is due to irregularity of the pupil, but it may be seen when the latter is not very pronounced.

Light Reaction.—With two exceptions (Cases 14 and 15), contraction of the pupil to torch light was lost in all cases. These exceptions concerned, first, one eye of a bilateral disorder in which the pupil was irregular and showed a slightly delayed relaxation after convergence—evidently a very early change—and, secondly, one eye of another bilateral case in which exposure to torch light provoked slight but otherwise normal pupillary contraction. This pupil contracted and relaxed slowly with convergence.

It is well known that the tonic pupil may dilate in the dark and then slowly contract on re-exposure to daylight. The existence of this latent light reaction can be more easily demonstrated by exposing the pupil, in a dark room, to intense illumination. A 100-watt electric lamp at a distance of 6 to 8 inches from the eyes was used for this purpose. This resulted in a definite tonic reaction, that is, a slow contraction and relaxation, in twelve eyes and a doubtful one in two other eyes. In a single instance the response was normally brisk and relaxation was not slow, although there was no contraction to torch light. In four eyes there was no response to such an intense stimulus, nor did these pupils dilate in the dark; light rigidity in these cases was complete.

When the duration of the reaction was timed, it was found that contraction and relaxation were usually affected unequally and that either movement might be slower than the other. More commonly relaxation was the slower movement, but in four eyes it occurred at greater speed than the preceding contraction. This latter finding was unexpected, as it is commonly asserted that one of the essential features of the tonic reaction is that relaxation is slower than contraction. In no case was this tonic light reflex excessive in amount; in unilateral cases the final size of the pupil was always larger than in the normal eye.

There is therefore no typical reaction of the tonic pupil to light. In the early stages of the disorder when other pupillary reactions are tonic it may still be normally brisk. On the other hand it may be completely unreactive to light or shade. Between these extremes most cases will show evidence of "tonicity" but only when intense illumination is used. With a weak stimulus (torch light) no contraction is usually visible. It may be noted that in no case was the light response the only pupillary movement to be affected.

The Convergence Reaction.—A tonic pupillary reaction on convergence of the eyes was found in all except one case. This patient (Case 6) had a dilated pupil, fixed to light and convergence, but showed a slowness of accommodation. With this exception each of the twenty-two eyes showed what has usually been regarded as a typical response—a slow contraction and an equal or usually greater sluggishness of relaxation. It is difficult to know what should be regarded as the normal maximal times for these movements. Case 14, where a relaxation of 1 mm. took 4 seconds, and Case 13, where a relaxation of 1·5 mm. took 5 seconds, have been regarded as showing slight but definite evidence of abnormality. In each of these cases the opposite eye showed a more pronounced reaction. Where movement is very slow

it is extremely difficult to time the end point in either direction with precision, and frequently several attempts are necessary to obtain even an approximate result. Within these limitations the range of values has been : for contraction normal (2) to 90 seconds ; for relaxation 4 to 135 seconds (all measurements by stop watch). Only exceptionally did contraction take longer than 20 seconds or relaxation more than 40.

Adie claimed that *delay* in addition to slowness of movement was the essential feature of the tonic reaction. Again, accurate assessment is difficult and probably necessitates the use of a slit lamp, which was not used in this series ; but the impression gained has been that such delay is rather unusual and that when it occurs it is more frequently seen at the beginning of contraction than at the commencement of relaxation. It is certainly not always seen.

One other feature of the convergence reaction has often been stressed, namely, the excessive contraction which may, so it is said, continue even after convergence has been relaxed. Miosis, by which is meant a pupil of 2·5 mm. diameter or less, was produced with convergence in eight affected pupils (Cases 3, 9, 10, 13, 14, and 15). However, the resting diameters of the pupils in these cases were never greater than 4 mm. and, since in normal eyes convergence may result in a contraction of one third of the resting diameter (Kestenbaum, 1947), this miosis may fairly be regarded as not very excessive. In only one of the eight unilateral cases (Case 3) was the affected pupil smaller than the normal one at the end of convergence. Continuation of contraction after cessation of convergence was never seen, and it seems doubtful whether this ever occurs.

If we exclude phases of the disorder in which the pupil is dilated and fixed it would seem from this series that the essential feature of the tonic pupil is its failure to dilate promptly when the eye relaxes from a convergence movement. This may be the only evidence of " tonicity " of the pupil and it clearly is the main justification for the term, because sluggishness of contraction may be, in fact, purely a paretic dysfunction. Just as it is probably the earliest tonic feature, so it is usually the most pronounced one in a temporal sense, being almost always of longer duration than contraction. The two movements may sometimes be equally slow, but relaxation is never faster than contraction.

Accommodation.—Defective accommodation and ipsilateral frontal headaches are the only ocular symptoms produced by the condition. They occur in a few patients. In these cases the onset is fairly abrupt, the patient noticing that he cannot see objects clearly for a brief period immediately he looks at them. More frequently near objects only are affected in this way ; less commonly distant objects are transiently blurred. Power of accommodation may also be weakened as well as delayed and the near point of the eye may recede.

These symptoms are associated with an enlargement of the affected pupil and they may disappear after a period of weeks or months although the latter remains. On the other hand, defects of accommodation which have never been appreciated by the patient may be found on routine testing.

Accommodation was tested by first measuring the near point of the eye. Then a Jaeger test type which could be read comfortably at a distance greater than this (usually J4 to J8 at 30 cm.) was held between the patient's eye and a distant object (a chimney pot about seventy-five yards away) seen through the window of the room. He was asked to look from one to the other as the test type was removed or replaced and to say immediately when the near or distant object became sharply focused. Any delay was timed by a stop watch. Normally there is no measurable delay. In all except six eyes some delay was found by this method. In the sixteen eyes in which such tonic accommodation was present the delay was found on looking only from the far to the near object in thirteen cases ; only from the near to the far object once ; and in both directions twice. These results are unusual in two respects ; first, in the matter of their frequency, for disturbances of accommodation are generally assumed to be relatively uncommon in this condition ; and, secondly in the fact that delay in focusing was most commonly seen only when a near object was being looked at, that is, during active contraction of the ciliary muscle. Slow relaxation of this muscle was rare, a finding at variance with what is commonly described. Delay in accommodation was, therefore, usually the result of a feebleness of action of the ciliary muscle. In spite of this, however, paresis of accommodation, as judged by a near point greater than 20 cm., was seen in only five eyes, Cases 8 and 10 being most definite. This slowness of accommodation was never as great as the corresponding slowness of the sphincter muscle during convergence. It varied from 1 to 6 seconds.

In contrast, therefore, to the convergence reaction, true tonicity, that is, delayed relaxation, of accommodation is less frequently seen than simple sluggishness of ciliary contraction. The latter is analogous to the few instances in which contraction of the pupil to light was more delayed than subsequent relaxation.

Adie stated that isolated tonic accommodation was unknown. This is confirmed in the present series and no such cases have been found in the literature. In all the sixteen eyes mentioned above there was a tonic reaction on convergence and an absent or tonic light reflex, with the exception of Case 6 in which the pupil was fixed both to light and on convergence. In this patient accommodation for near vision was delayed 5 seconds and there was a paresis of accommodation (near point 29 cm.).

In brief, therefore, disturbances of accommodation are common, though they are often unnoticed by the patient, and a slowness of contraction of the ciliary muscle is found more frequently than a slowness of relaxation. These changes are never seen in isolation, and their only practical value is in the diagnosis of the type of tonic pupil which presents as a dilated and fixed pupil.

Other Pupillary Reactions.—When the eyes are tightly closed the pupils may contract in normal persons. Usually, however, they dilate, owing to the removal of the light stimulus. Whether the former reaction occurs probably depends on whether the eyes converge behind the closed lids. Similarly tonic pupils may contract when the eyes are closed. This, as in the normal case, is relatively uncommon, having been seen only on three occasions in the series. In bilateral cases it may be more marked in one eye than another. Once contracted the pupil shows the same delay in relaxation as after voluntary convergence. In most cases, however, the tonic pupil remains unchanged in size during firm lid closure.

Both Holmes and Adie mention that the pupil may contract during crying. This was seen on one occasion in Case 12, a child aged 12 who became alarmed and tearful when told that drops were to be put in her eyes. Both pupils, from being widely dilated (9 mm.), soon contracted down to 7 mm. and slowly dilated after her sobbing had ceased. Unfortunately this was not timed. Presumably this pupillary reaction is part of a more widespread parasympathetic discharge which occurs in crying.

Reaction of the Pupil to Drugs.—The tonic pupil reacts normally to the conjunctival instillation of homatropine and eserine. Alajouanine and Morax (1938) go further and state that in every case there is a " precocious " reaction, dilatation or contraction occurring more rapidly in the affected eye than in the normal eye. Lowenstein and Friedman (1942), moreover, found that at a certain stage of the contraction of the pupil to eserine the light reflex returned. Neither of these observations has been confirmed. In two bilateral tonic pupils (Cases 11 and 15) homatropine did not produce full dilatation in one eye. In all other cases tested, normal results were obtained.

Scheie (1940) reported a series of six patients in all of whom contraction of tonic pupils occurred with a 2½ per cent. solution of *acetyl B methyl choline* (" Mecholyl "), a concentration too weak to affect a normal pupil. His results are confirmed by Walsh (1947), who considers the test of great diagnostic value. A 2½ per cent. solution of " Amechol " (Savory and Moore) was used on all patients—2 drops from an unstandardized dropper being placed in each eye. A contraction of 1 mm. after 30 minutes was seen in four eyes ; of 1·5 mm. in 2 ; of 2 mm. in 1 eye ; of 2·5 mm. in 1, and of 5·7 mm. in 2. No response was found in twelve eyes. The response is therefore variable, but the test is worth applying for a positive result is of great help when the diagnosis is in some doubt.

When contraction occurred with this drug there was no change either in the light reflex or in the pupillary response to convergence, but in one patient (Case 12) the delay of accommodation was abolished and the near point of the eyes reduced, and in another (Case 6) the delay in accommodation was reduced.

Associated Loss of Tendon Reflexes.—Of the fifteen patients studied, twelve had absence of one or more reflexes, one had a sluggish right ankle jerk, and in only two (Cases 2 and 8) were the reflexes normally brisk.

Associated Symptoms.—Apart from blurring of vision and ipsilateral headaches, the Holmes-Adie syndrome is generally considered to be asymptomatic. Holmes (1931), it is true, mentioned the occurrence of mild pains and paræsthesiæ in the limbs at the time of onset of the pupillary disturbances, but Adie did not refer to them. French writers, however, have frequently stressed the existence of obscure pains in many patients with this syndrome, pains which can be related neither to the pupillary or the reflex changes. Aching pains, muscle stiffness, cramps, and even sharp stabbing pains of a lightning type have been described in the limbs. Severe localized or generalized headache of both migrainous and non-specific type and unrelated to the pupillary abnormality, anginal chest pains, and pains in the throat and neck have also been reported (Barré and Klein, 1934 ; Lhermitte, 1937 ; Alajouanine and Morax, 1938 ; Sigwald, 1941).

Careful inquiry in this group of patients revealed that such symptoms are, in fact, not uncommonly experienced (Cases 6, 7, 9, 14, and 15). Their

nature is quite obscure, and they may sometimes add yet another difficulty to the differentiation of the condition from neurosyphilis.

Diagnosis

From the experience of these cases it would seem that there are two types of tonic pupil.

The "Fixed" Type.—This is the less common variety. Here the disturbance is unilateral and the affected pupil is larger than normal, irregular in shape, and totally unresponsive to light or convergence. The only means of distinguishing it clinically from a complete ophthalmoplegia interna is by testing the accommodative mechanism. In the tonic pupil this is usually not paralysed completely and may show slowness of contraction or, less often, of relaxation. Such a pupil may contract under *acetyl B methyl choline* and this may help in differentiation. This type may change after a varying period into the second type.

The "Ordinary" Type.—Here the disturbance may be unilateral or bilateral. The pupil may be of any size; it is irregular in shape, and often eccentrically placed in the iris. The essential feature is a slowness of dilatation after convergence. This is always present, and may be the only evidence of abnormal pupillary movement in the early stages. Usually, however, contraction on convergence is also slow and is sometimes both delayed in onset and excessive in amount. In this type the light reflex may be normal in the early stages, but later is either completely absent or may show a slowness of contraction and relaxation when intense illumination is applied. Tonic accommodation may or may not be present. The various combinations of reactions which may, therefore, occur are numerous, so much so that Adie's classification into "typical" and "atypical" phases seems unjustified. The only typical features in the sense that they are always seen in this second type are (*a*) the irregularity of the pupil, and (*b*) the slowness of relaxation after convergence.

Comparing these changes with what may be seen in the pupil in neurosyphilis there are several obvious points of similarity. In both the pupil may be irregular, it may be of any size, and it may show no response to light. Contraction of the pupil on convergence may be sluggish but when this happens in neurosyphilis the subsequent dilatation is normal, whereas in the tonic pupil it is always more delayed. This is the most important distinguishing feature and the surest way by which the two conditions may be differentiated by simple clinical examination.

In the phase of the fixed dilated pupil differentiation is more difficult and depends on the recognition of tonic accommodation. Should this be absent, then full laboratory investigation of blood and cerebrospinal fluid may be required.

Pathology of the Tonic Pupil

The tonic pupil in Adie's view was "a benign disorder *sui generis*" and since his time, although no pathological studies have ever been made and no cause has ever been advanced to account for it, it has been regarded in this country as an innocent condition with probably a uniform ætiology. A perusal of the literature, however, suggests that such a view is not altogether supported by experience.

Before and since Adie's publication cases of tonic pupil have been recorded in association with other diseases, for example, trauma (Axenfeld, 1906; Oloff, 1914; Roemheld, 1921), diabetes (Nonne, 1902), and malignant basal intracranial tumour (Garcin and Kipfer, 1936). In the present series of cases there is one (Case 8) where the tonic pupil was a direct and isolated sequel to a head injury. Tonic pupil has also been described as a familial disturbance (Dressler and Wagner, 1937; McKinney and Frocht, 1940), and Lowenstein and Friedman (1942) report slight pupillary abnormalities in the mothers of some of their patients.

Discussion has principally centred on whether a tonic pupil may be caused by neurosyphilis. Such a possibility has never been accepted in this country, notwithstanding the difficulties that may arise in distinguishing the two conditions. In France, however, several cases have been described in which cerebrospinal fluid changes and a positive Wassermann reaction in the blood have been found. These are enumerated in the paper of Alajouanine and Morax (1938), the most comprehensive one on the subject yet written. These authors record eight personal cases of tonic pupil, of which they consider one was certainly due to syphilis and three others probably so. They stress the point that in their own and other cases the infection has been of very long standing and frequently hereditary in origin. Though the total number of such cases is small, and coincidence, therefore, cannot be ruled out, it seems justifiable to entertain the possibility that occasionally syphilis may be the cause of the tonic pupil. As a morbid physiological entity it would indeed be surprising if it had a single pathology, and if this be admitted there seems no reason why syphilis should not occasionally be the cause.

In practice, however, the vast majority of cases are of unknown ætiology, and adequate observation over long periods of time has shown that the disorder is not the result of any progressive neuro-

logical disease. With the one exception mentioned, no cause was found for the disorder in any of the present cases.

The Anatomical Site of the Lesion

Several suggestions have been made about the possible site of the lesion causing a tonic pupil. The absence of any post mortem confirmation renders discussion purely speculative, but in spite of this the clinical features of the condition, when critically considered, limit the possibilities to a greater extent than theories have hitherto suggested. Five sites have been postulated: (1) the supranuclear oculomotor pathways (Lowenstein and Friedman, 1942), (2) the hypothalamus (Kennedy and others, 1938), (3) the third nerve nucleus (Adie, 1932; Behr, 1921), (4) the ciliary ganglion and/or the ciliary nerves (Magitot, 1911), and (5) the sphincter muscle (Saenger, 1902).

Of these hypotheses, (1) and (2) may be dismissed at once for the absence of a light response in a unilateral tonic pupil with the retention of a consensual reaction in the normal pupil places the lesion on the efferent limb of the light reflex arc. Saenger's suggestion that the condition is a disorder of the sphincter muscle analogous to the myotonia of Thomson's disease may likewise be eliminated. The not infrequent absolute rigidity of the pupil to light, and less often to convergence, together with its normal contraction when stimulated directly by pilocarpine, clearly indicate that the lesion is in the nervous pathways controlling pupil movement.

It seems most likely, therefore, that the lesion affects either the vegetative portion of the oculomotor nucleus or some part of the peripheral path of its emerging fibres. At this point argument is hampered by a lack of precise anatomical knowledge concerning the origin and course of fibres which control the pupillary reflexes. It is generally agreed that the Edinger-Westphal nucleus is the origin of fibres which subserve the light reflex. These run to the sphincter muscle via the ciliary ganglion and the short ciliary nerves. They are usually described as being unilateral in distribution. Langworthy and Ortega (1943), however, state that each nucleus supplies fibres to both oculomotor nerves. If this is so, then unilateral disorders of the light reflex can only arise from peripherally situated lesions. If not, however, it is conceivable that the changes seen in the tonic pupil may have a central cause.

Greater obscurity surrounds the pathway of fibres which govern reflex pupillary contraction on convergence of the eyes. Its origin is depicted sometimes as the caudal end of the Edinger-Westphal nucleus, sometimes as the median nucleus of Perlia whence fibres run to both oculomotor nerves. Their peripheral pathway is unknown, but they probably do not pass through the ciliary ganglion. Foerster and others (1936) have shown that removal of this structure in apes abolishes the light reflex but not pupillary contraction on convergence. In man, Nathan and Turner (1942) have similarly reported isolated light rigidity of the pupil following head injuries in which it seemed reasonably certain that the traumatic lesions were peripherally situated. They suggest that convergence fibres may relay in the episcleral ganglia of Axenfeld which lie in the scleral canals in close proximity to the short ciliary nerves.

In the midst of this anatomical uncertainty, any attempt to localize further the site of disturbance of the tonic pupil must remain hypothetical. There seem to be valid reasons, nevertheless, for rejecting Adie's theory of a central nuclear disturbance. The term tonic pupil conjures up an idea of pupillary rigidity dependent on excessive tone preventing sphincter movement. Adie (1932) for instance, speaks of a pupil "so stiff that at the time of examination no reaction to light or on convergence is obtained" and, again, visualized stimuli "stored in excess and slowly liberated" from the cells of the oculomotor nucleus so producing slowness of contraction and relaxation. These two ideas are mutually exclusive since the first would depend on an excessive and continuous sympathetic tone, whilst the second implies a continuous parasympathetic discharge.

Moreover, since, as we have seen, a tonic pupil may be persistently larger or smaller than normal and is always irregular, it is difficult to conceive how these various changes may result from a nuclear lesion.

We are therefore left with the hypothesis that the lesion lies in the peripheral oculomotor pathway viz. in the ciliary ganglion or the short ciliary nerves—a suggestion first made by Magitot (1911) and lately revived by Scheie (1940) and Leathart (1942). There is much to recommend this idea, though in its simplest form it fails to explain all the changes seen. Scheie suggests that there is an incomplete interruption of transmission in the ganglion or nerves which accounts for the sluggishness or absence of pupillary contraction. He further suggests that this partial interruption of conduction results in a slow liberation of acetylcholine at the myoneural junction which diffuses through the sphincter muscle and so hinders its relaxation. If this were so it might be expected that pupillary contraction would start in isolated segments of the iris and spread slowly to neighbouring ones. In fact no such movement occurs. When contraction occurs the iris widens more or less

uniformly so that the irregularity of its margin remains unchanged. Nevertheless the implication of Scheie's suggestion, namely that there are probably two fundamentally distinct changes, one in the peripheral nerve the other at the myoneural junction, seems a new and fruitful approach to the problem.

We have seen that sometimes light rigidity of the tonic pupil is complete and that there may be no movement of the pupil with ocular convergence, no matter how intense the stimulus may be. There is, in fact, in such cases a paralysis of the sphincter muscle and the pupil is dilated. This can only be the result of an interruption of fibre conduction. In less severe cases the pupil contracts only under intense illumination and does so slowly. This suggests a partial interruption of conduction in the efferent fibres, and we may suppose that usually this affects the short ciliary nerves to a greater extent than the still hypothetical convergence fibres, for in most cases convergence results in pupillary movement when the light reflex is completely or almost completely absent. The irregularity of the pupil may be explained by supposing that these changes do not affect the ciliary nerves uniformly.

Sluggishness of contraction is, therefore, merely an indication of a partial interruption of conduction in the efferent fibre. But delayed conduction will not explain slowness of relaxation. Here we must assume a functional disturbance at the myoneural junction ; that, just as there is a slow liberation of acetylcholine, so its destruction by cholinesterase is delayed. The contraction of a tonic pupil produced by concentrations of *acetyl B methyl choline* which are too weak to affect normal pupils lends support to this suggestion, for in normal eyes this substance is presumably destroyed by the cholinesterase present.

It is, therefore, possible to construct a plausible working hypothesis concerning the underlying physiopathological disorder which results in a tonic pupil. There is, first, a disturbance of conduction in pupillomotor fibres, and secondly an alteration in the chemical changes resulting from such stimuli at the myoneural junction. Possibly the latter is a sequel of the former. The conduction defect occurs in the short ciliary nerves conveying the light reflex fibres and, to a greater or lesser extent, in the still unknown convergence reflex fibres. As a result of this the pupil may become completely immobile. More often its response to light is impaired and sluggish so that it may only contract slowly on exposure to a strong source of illumination, whilst its contraction on convergence, although slow, is more readily demonstrable. At the same time a delay in the destruction of acetylcholine at the myoneural junction prevents normal relaxation and results in slowness of dilatation after the pupil contracts. This is best seen with the convergence movement which is a stronger stimulus to pupillary movement. Such a biochemical change may fluctuate and be responsible for the occasional variable size of the tonic pupil from day to day.

The site of the lesion producing a tonic pupil is therefore, on this view, at the efferent end of the pupillary reflex pathway. Circumstantial evidence supporting this is found in the occasional occurrence of a tonic pupil after orbital injuries. Such cases have been recorded by Axenfeld (1906) and Ohm (1907).

If this hypothesis is correct it follows that the tonic pupil should always be larger than normal. In most cases this is so, but occasionally it may be smaller and sometimes even miotic. In such cases there may be, in addition, a paresis of the dilator mechanism, and it may be that the same process that attacks the parasympathetic fibre spreads to adjacent sympathetic nerve endings. The very occasional occurrence of a partial ptosis in association with a tonic pupil (Alajouanine and Morax, 1938 ; Moore, 1931) supports such a view.

The very frequent association of the tonic pupil with absent tendon reflexes raises the suspicion that the two phenomena have a common pathological cause and a similar underlying anatomical or biochemical defect. Tendon areflexia in such cases is unaccompanied by any of the objective motor or sensory changes, which in other diseases help to determine the site of the lesion causing loss of reflexes. This isolation of the absent reflex, however, may possibly be a point in favour of regarding it as being due to a peripheral defect. Whether this lies on the sensory side of the reflex arc, whether, for example, there is some change in the stretch receptors, or on the motor side, as for instance in the motor fibre or at the myoneural junction is, however, quite unknown. Arguing by analogy from the probable site of the lesion causing the tonic pupil, it seems perhaps more likely that the lesion is in the motor pathway, but this conclusion is purely a speculative one for as yet we possess no knowledge, either clinical or pathological, to help in the elucidation of this problem.

Summary

1. Fifteen patients with tonic pupils have been studied. The variability from case to case of the abnormal pupillary reflexes is stressed ; no single combination can be regarded as typical.

2. Two types of tonic pupil may be distinguished (*a*) the fixed type, and (*b*) the ordinary type of tonic

pupil. The only features common to all examples of this latter variety are (1) the irregularity of shape or position of the pupil and (2) the slowness of pupillary dilatation after convergence.

3. Defects in accommodation are common and often pass unrecognized.

4. The possible anatomical site of the lesion causing the tonic pupil is discussed.

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CLINICAL AND PATHOLOGICAL OBSERVATIONS ON RELAPSE AFTER SUCCESSFUL LEUCOTOMY

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Return of mental symptoms after their disappearance or marked amelioration for a substantial period following bilateral frontal leucotomy has been described in a small proportion of cases by most psychiatrists who have published a detailed analysis of their postoperative clinical results. Nowhere in the literature, however, has the occurrence of relapse after recovery been correlated with the actual position and dimensions of the leucotomy lesions as established after death. The main purpose of the present paper is to describe the anatomical findings in the six most striking cases with a history of such a relapse out of the leucotomy brain material and case records being collected at the Maudsley Laboratory, and to discuss practical and theoretical implications of the findings in these cases and others in the literature in which the surgical damage can be reliably evaluated. Some clinical features of these and other relapsed cases in the literature of "psychosurgery" can conveniently be discussed at the same time.

Material

Summarized clinical histories of the six cases are given below, together with a description of the leucotomy cuts as found after fixation of the brains. The data most relevant to the discussion are further summarized in the Table. Details of premorbid personality and of body build were unfortunately lacking in most of the case records. The terms used in describing the position and extent of cuts are defined in Figs. 1 and 2.

CASE 1

Pre-operative History.—A.B. was an only child of parents of mentally healthy stock. His early development was normal. At school he was outstanding in art and sport. After three and a half years in various clerking jobs he volunteered for the R.A.F. at the age of 19, became an air gunner, was awarded the D.F.M., and had completed fifteen operations at the time of his breakdown in 1943. He had had no previous illness except rheumatic fever at the age of 12. His premorbid personality was described as intelligent, energetic, steady, reliable, and open; a good mixer, fond of sport and ambitious in art; normally hetero-sexual. He was athletic in body build, with a strong masculine face.

In October, 1943 at the age of 23 he began to have feelings of inadequacy. He came to believe that he had an obviously weak chin and that people could see by his face that he was homosexual. He developed sniffing and snorting movements which distorted his facial appearance. After unsuccessful psychotherapy in a military psychiatric hospital he was boarded out of the R.A.F. in July, 1944. He became rapidly more tense and agitated and later that same month underwent leucotomy. No detailed record of investigations before operation can be traced.

Leucotomy.—Subsequent laboratory investigation of the brain revealed the smooth-walled slit-like lesions to be practically symmetrical, unusually rostral, and limited to involvement of the dorsal segment of white matter on the left side and to the dorsal segment and an adjacent part of the central segment on the right side. Fig. 3 illustrates the position of the entry marks and the plane and extent of the cuts in relation to the frontal convolutions and Brodmann's areas.

Postoperative History.—Immediately after the operation he felt extremely well, his mannerisms ceased, and he was aware of heightened libido leading to increased sexual activity. His parents noted that he was more confident, more active, and more ambitious than before the illness. Assisted by a Government grant he took a two-year course in commercial art; but, failing to obtain work of that nature, he returned to clerical employment in September, 1947. He became gradually discouraged, and in February, 1948 broke off an engagement to marry. In March, 1948 all his previous symptoms began to return, and when he was readmitted to hospital in July, 1948 his condition was as bad as it had been before operation: he was sniffing and snorting; unhappy, tense, impatient, and resentful; talking rapidly and at great length of his delusions (such as one of reference to his homosexuality when, in Switzerland in July, 1948, he thought he heard a foreigner calling him "Herr Si-si"); banging on the table to emphasize his points; and demanding another operation on his brain or else he would kill himself. His I.Q. was found

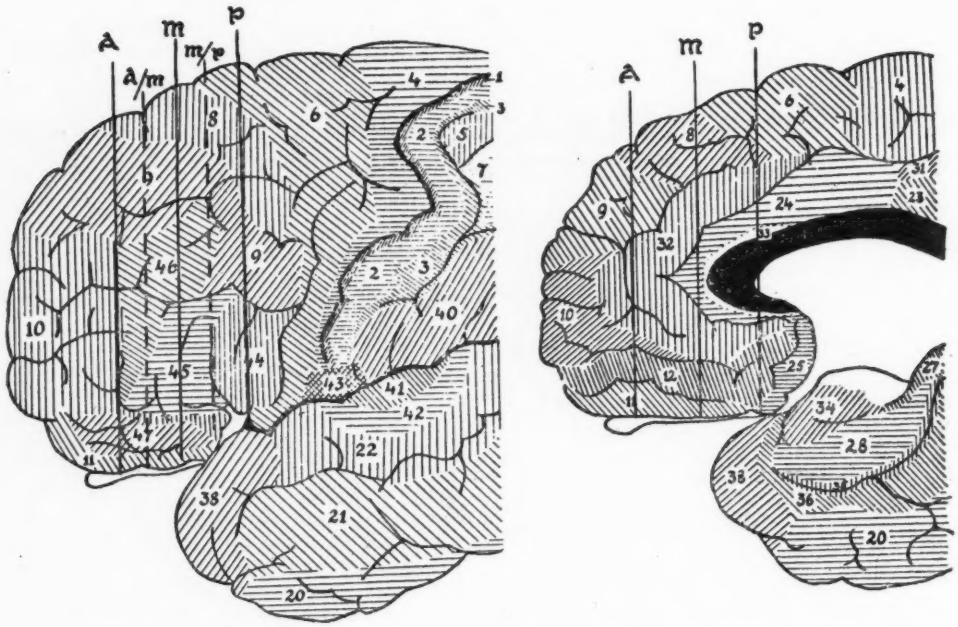

FIG. 1.—" M " denotes the plane perpendicular to the orbital plate and passing through the centre of " pars triangularis " (area 45), the usual leucotome entry point aimed at in this country. Planes A and P lie 1½ cm. anterior and posterior respectively to M, A/M and M/P midway between. When the leucotomy lesion is cystic, curved, or oblique, its mean plane is utilized in summarized descriptions.

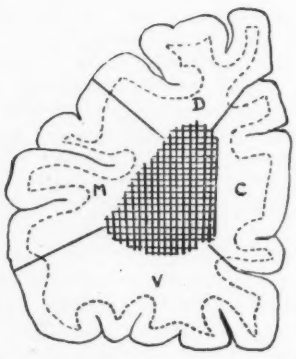

FIG. 2.—Five segments of white matter are differentiated in the coronal plane: D=dorsal; M=middle; V=ventral; C=cingulate; Hatched=central. Involvement of a segment is recorded as positive when a majority of the fibres in it are cut.

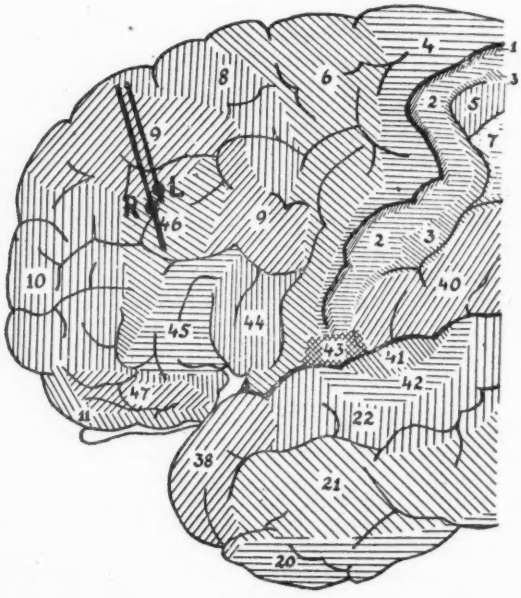

FIG. 3.—Case 1.

to be 114 on the Matrix test and 127 on the Mill Hill Vocabulary. He was diagnosed as being in a mixed state with depressive and paranoid features.

His excitement settled rapidly in response to reassurance and conservative measures. He became cheerful, hopeful, and less insistent about his delusions. At occupational therapy he displayed creative artistic ability which seemed unimpaired in every respect when compared with his productions at art school and during his premorbid period. He began to make reasonable plans about his work and marriage. On Sept. 8, 1948, his fiancée was found to be pregnant. On Sept. 13 he quarrelled with his parents about the marriage. Next day he escaped from hospital, went home, and committed suicide by taking aspirin ; this was four years and two months after the date of the leucotomy.

CASE 2

Pre-operative History.—B.C. was a married man who, at the age of 56, after being unusually quiet and thoughtful for five months, developed such severe depression and apathy of mood with delusions of poverty and ruin as to require hospitalization. He remained in this mental state for five years, physical therapy being precluded by complications following a surgical operation for retention of urine. He then received two electric convulsions and became much improved in mood. Because of symptoms of compression of a lumbar vertebra the projected course of treatment had, unfortunately, to be stopped, and he rapidly relapsed into his previous state.

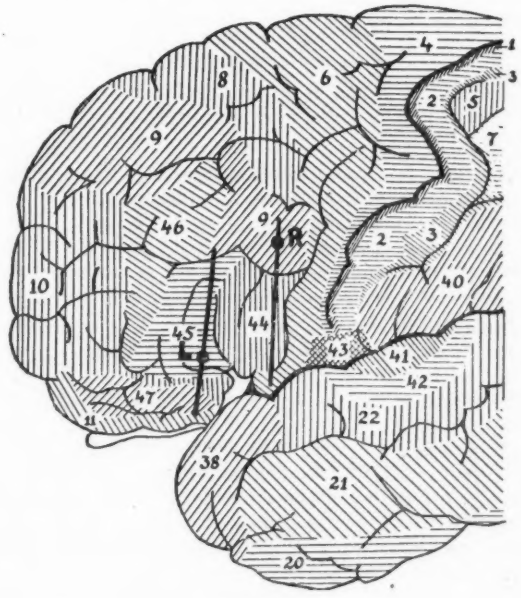

FIG. 4.—Case 2.

Leucotomy was performed five years and eight months after admission to hospital. Subsequent laboratory investigation of the brain revealed the left leucotomy scar to involve a major portion of the central, ventral, and cingulate segments of white matter in plane M ; the right scar involved a large proportion of the central, ventral, and middle segments in plane P (Fig. 4).

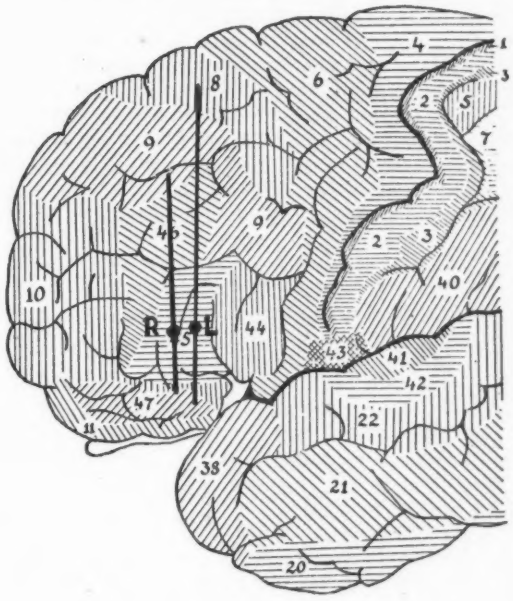

FIG. 5.—Case 3.

Postoperative History.—He made such rapid full recovery to his normal cheerfulness of mood and physical activity that he was discharged home three months after the date of operation. His recovery was fully maintained until one year and five months later, when he developed a severe carbuncle, relapsed completely to his pre-operative mental state, persuaded his doctor and wife not to let the hospital know of his condition, and committed suicide a month later, one year and nine months from the date of operation.

CASE 3

Pre-operative History.—C.D. was a youth of athletic physique who at the age of 19 after a homosexual incident developed mild paranoid schizophrenic symptoms whilst on overseas service, responded successfully to a course of cardiazol shock treatment, and returned to his duties as a private soldier for four years. Almost immediately after his discharge from the Army (on physical grounds) in August, 1944 he was observed to display delusions of reference and persecution, fears of insanity, and attacks of trembling. During the succeeding months he became tense, agitated, depressed, and acutely suspicious. Shock therapy was apparently not repeated.

Leucotomy was performed seven months after the onset of the acute recrudescence. Subsequent investigation of the fixed brain showed both cuts to lie in plane " M," the left one affecting all five segments of white

matter, the right one sparing the dorsal and cingulate segments (Fig. 5).

Postoperative History.—After a postoperative hypomanic phase of three weeks' duration his mood returned to normal, his delusions faded, and he was discharged recovered at the end of two and a half months. In character he altered for the worse, becoming completely irresponsible and untruthful, but he worked satisfactorily as a night porter for one year without evidence of delusions. He then gave up work through laziness, gradually relapsed into a state of moody abusive suspicion, and had to be re-certified. A year later, no improvement having occurred in response to psycho-

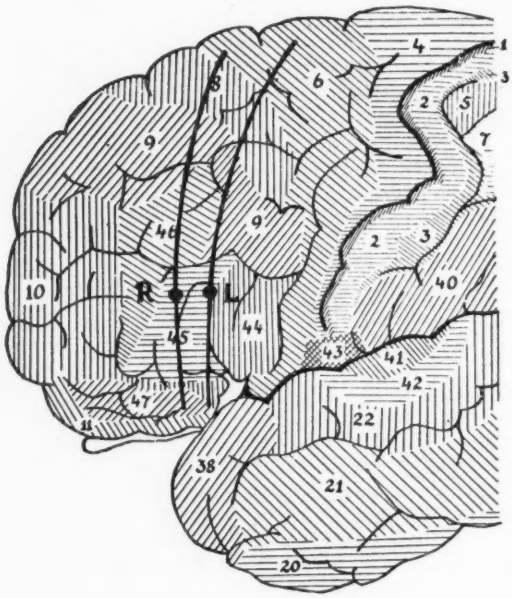

FIG. 6.—Case 4.

therapy, insulin coma treatment was started. His behaviour had become rather worse when, during the fifteenth treatment, coma became irreversible and he died, two and a half years from the date of operation.

CASE 4

Pre-operative History.—D.E. was a very over-dependent hypochondriacally-inclined domestic maid who, at the age of 19 and without apparent cause, became depressed with delusions of reference and attempted suicide. She improved for about four months after a course of electric convulsions (E.C.T.), but two months later was described as sullen, suspicious, and impulsively aggressive, with auditory hallucinations. She now failed to respond to courses of E.C.T. and of continuous narcosis. A course of insulin coma rendered her quiet, amenable, and employable for one month. She then relapsed completely and remained resistive, restless, and violent in her behaviour without remission until operated upon eighteen months later.

Leucotomy was performed two years and ten months after the onset of illness. Subsequent investigation revealed the symmetrically curved left and right lesions to involve all five segments of white matter at the level of planes M/P and M respectively (Fig. 6). The only white matter entirely spared was that of the rectal gyri.

Postoperative History.—On recovery from the operation she was quiet and rational and remained so until discharged "recovered" at the end of two and a half months. She resumed her previous occupation successfully for two months, and then relapsed rapidly into her pre-operative state. She now, however, responded so well to superficial psychotherapy that six months later she was able to return home and to her work again for a period of nine months. She was then jilted by a man by whom she feared she was pregnant and relapsed rapidly into a more suspicious, impulsively violent, and destructive condition than ever before. Three months later she suffered a major epileptic fit, six months later a second one, and two months later a third one in which she died, two and a half years from the date of her operation.

CASE 5

Pre-operative History.—E.F. was an asthenic nervous overprotected young woman who at the age of 25 developed fits of depression with obsessional rumination about religious topics and fear of suicide. In spite of intensive out-patient psycho-therapeutic and physical treatment throughout the following four years her symptoms became gradually more severe. At the end of that period an in-patient course of insulin shock failed to produce change and a further course of E.C.T. only converted her mood from depression to hypomania without modifying her obsessional rumination or now ritualistic behaviour.

Leucotomy was performed four and a half years after the onset of the illness. Subsequent examination of the brain showed the major portion of all five segments of white matter in each hemisphere to be involved in the lesion, at plane M (Fig. 7). Only the white matter of gyrus rectus on either side was wholly spared.

Postoperative History.—She suffered some permanent loss of spontaneity but showed a gradual improvement in her mental symptoms for four months. At the end of this period her obsessional ideas and actions were much less vivid and absorbing than before and she was discharged home. About five months later she started to regress gradually to her pre-operative condition. Intensive psychotherapy produced no improvement, and ultimately electro-narcosis was initiated. During the fourth treatment she suffered irreversible syncope and died, two years from the date of operation.

CASE 6

Pre-operative History.—F.G. was a young married woman who at the age of 30 rapidly developed a state of seclusive negativistic mutism alternating with spells of agitation with delusions of reference and persecution. Three years later her excited phases became very violent

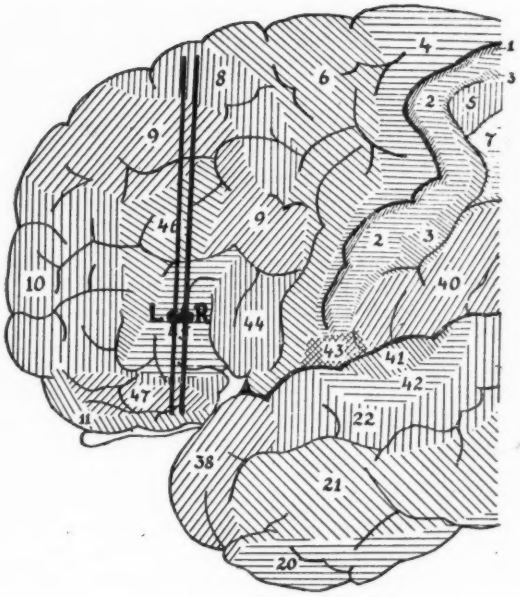

FIG. 7.—Case 5.

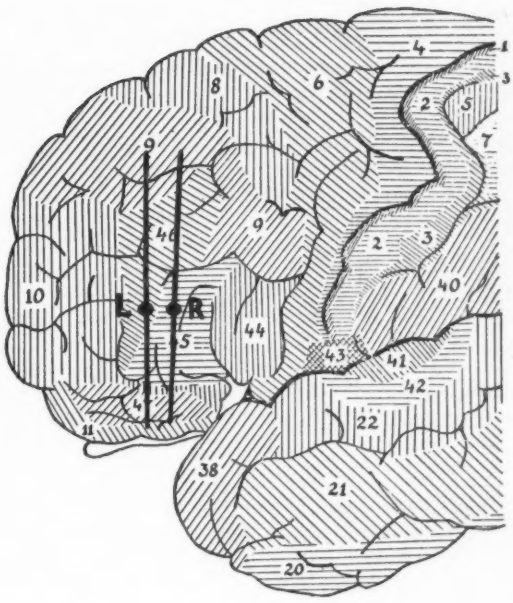

FIG. 8.—Case 6.

TABLE

SUMMARY OF DATA FROM CASES 1 TO 6

Case No.	Main pre-operative symptoms	Duration of illness	Plane of cuts		Segments cut (out of 10)	Duration of recovery	Environmental factor in relapse
			L.	R.			
1	Delusions of reference and unworthiness ; agitated depression ; facial tics	9 mths.	A/M	A/M	3	3 yrs. 8 mths.	+
2	Depression ; delusions of poverty and sin	5 yrs. 8 mths.	M	P	6	1 yr. 8 mths.	+
3	Paranoid delusions ; tenseness ; agitation	7 mths.	M	M	8	1 yr. 3 mths.	–
4	Paranoid delusions ; auditory hallucinations ; violence	2 yrs. 10 mths.	M/P	M	10	1 yr. 1 mth.	+
5	Obsessional rumination and activity ; depression	4½ yrs.	M	M	10	9 mths.	–
6	Catatonic phases of excitement and stupor ; no remissions	15 yrs.	A/M	M	8	2½ mths.	–

and destructive and her negativistic phases more acute. She was completely unemployable. Two years later delusions of grandeur began to appear during the excited phases. Three years later still her general habits began to deteriorate, and they continued to do so progressively for the next six years without remission.

Leucotomy was performed about fifteen years after the onset of illness. Subsequent investigation revealed the lesions to lie in planes " A/M " and " M " and to involve all except the dorsal segment of white matter and the medial orbital region on each side (Fig. 8).

Postoperative History.—For two and a half months after the operation she was well behaved, displayed a sense of humour and willingness to work for the first time since admission, was clean in her habits, and took an interest in her personal appearance. For no apparent reason she then suddenly relapsed to her pre-operative deteriorated psychotic state and remained so until her death from chronic phthisis one year and nine months after the operation. The remission was brief, but very striking when contrasted with her pre-operative history.

Discussion

Clinical Features.—Most writers have not given any clinical detail of their relapsed leucotomy cases, but Cook (1946) has described two patients with agitated depression who relapsed after one and a half years, and two with " somatopsychic " delusions who relapsed after four to five months; Frank (1946) referred to two paraphrenics who relapsed after one year and one aggressive psychopath who relapsed eight months after operation; and Garmany (1948) has reported an acutely obsessional patient with full relapse after complete postoperative recovery over a period of four years, and a catatonic who relapsed after three years of mental health. The types of mental symptoms and syndromes in these patients who suffered relapse and in the six under review comprise, therefore, most of the commonest components of the functional psychoses. Each symptom can apparently relapse to a degree of severity at least equal to its pre-operative intensity, " tension," the most generally agreed prognostic criterion for the operation, being no exception.

What is perhaps of more theoretical than practical importance is that in all the foregoing cases the symptoms that recurred were of the same kind as those present before operation. The only exceptions to this known to the writers are several cases of typical catatonic schizophrenia which Dr. L. C. Cook (personal communication) has observed to change after leucotomy into typical hebephrenic schizophrenia, and two instances in the writers' experience where a patient with an early-treated affective condition displayed, on relapse from moderate postoperative improvement, prominently schizophrenic features which had been present, but overshadowed, in the previous clinical picture.

A more practical consideration is that in Case 1 the circumstances of unsuccessful search for a congenial job and complications in love affairs seemed to play a determining part in the relapse: likewise the carbuncle in Case 2 and the jilting episode in Case 4. Frank attributed the relapse in one of his paraphrenics to harassing circumstances. Cameron and Prados (1948) likewise related the relapse, in five out of seven neurotic patients treated by gyrectomy, to the amount of stress after discharge. Hence environmental factors would seem able to play just as determining or precipitating a role in the ætiology of relapse after leucotomy as they can at the onset of illness. That they may indeed have stronger influence than before operation would seem suggested by the facts that in Case 1 and Case 4 of the present series the patient responded more favourably to psychological methods of treatment after relapse than before the leucotomy; the improvement in the paranoid state of another patient, not described here, was after operation so well maintained by E.C.T. that his case could be classified as one of aborted relapse; Liebert and Davis (1948) report one patient whom E.C.T. restored to normal mood only after postoperative relapse; and Fernandes and his associates (1948) mention four cases in which E.C.T., and one in which insulin therapy, became effective for the first time after relapse. It would appear, therefore, that there may be some general postoperative increased responsiveness to the environment which might allow considerable scope for prevention of relapse in at least a proportion of cases.

An additional point of interest in Case 1 is that the lesions " isolated " very nearly the same areas of cortex as Heath and Pool (1948), Mettler and others (1948), and Le Beau and others (1948a and b) have been ablating and which Freeman (1948) considers his transorbital leucotomy to isolate, namely dorsal areas 10 and 46 and anterior area 9 of Brodmann. The clinical status of the case falls within Freeman's criteria for good results after such rostral circumscribed cuts. It cannot of course be judged whether the illness might not have remitted spontaneously about the date of the leucotomy. This is a difficulty in evaluation which must beset all such early operative cases until large numbers, with fair controls, are available for statistical scrutiny. Another noteworthy feature of this case is that the personality change was of the euphoric type and not the akinetic (apathetic) type that would be expected by supporters of Kleist's (1937) concept of localization of functions within the granular frontal cortex. A further point of note is the

absence of appreciable deterioration in any component (as defined by Hutton and Basset, 1948) of the patient's artistic ability. This finding seems hardly consistent with Freeman and Watts's (1948) concept of localization of creative artistry in the polar regions, though it must be conceded that not the whole of the polar cortex was isolated in the present case.

Anatomical Features.—Four of the present cases (Nos. 3, 4, 5, and 6) can reasonably be described as having suffered practically complete bilateral isolation of the prefrontal cortex from its long fibre connections, gyrus rectus and posterior area 9 being the only regions consistently spared. The symptoms concerned in these four cases are fairly varied. Bilateral " isolation," therefore, of practically the whole prefrontal cortex does not prevent the remanifestation, after their relatively prolonged disappearance or striking amelioration, of many of the commonest psychotic symptoms. Hence, either the " isolated " cortex can in course of time become effectively reactivated through relays of subcortical U fibres, or through largely intracortical pathways, and can redetermine abnormal behaviour, or else psychopathological symptoms can develop anew without participation of the prefrontal regions.

That the former possibility may be the case is strongly suggested by the fact that degenerative nerve cell changes do not occur to any appreciable degree in the cortex rostral to the lesions (Freeman and Watts, 1942 ; Meyer and Beck, 1945). According to the theories associated with transneuronal degeneration this would imply that these nerve cells continue to derive stimuli from elsewhere than the cut corticopetal projection and association fibres. Again, and in full corroboration of the foregoing, the electro-encephalographic recordings from the prefrontal regions after leucotomy return to a relatively normal pattern after a period of from three weeks to three months (Cohn, 1945 ; Greville and Last, 1947), a duration which according to our experience coincides closely with the period of active absorption of blood and necrotic tissue within the scars.

That a patient completely deprived of his prefrontal regions may continue uninterruptedly to manifest at least some forms of psychopathological behaviour is demonstrated by instances of bilateral prefrontal lobectomy where the psychosis has persisted. Two such cases (both chronic deteriorated hebephrenic schizophrenias) have been reported by Peyton and his co-workers (1948) and Cook (personal communication) has one such patient, a chronic deteriorated catatonic, who has shown no improvement whatever. Again, there were, among those patients whose brains have been investigated at the Maudsley Laboratory, three suffering from chronic deteriorated catatonic schizophrenia in whom not even transient improvement followed full 9- to 10-segment cuts. It may not be without significance that all six of these patients were deteriorated schizophrenics.

Actual relapse from normality after apparently successful lobectomy has not yet been reported in the literature. In a personal communication, however, Drs. W. T. Peyton and E. W. Miller state that, of their series of fourteen lobectomy cases reported with Noran in February, 1948, they now (January, 1949) consider that one chronic catatonic schizophrenic patient (No. 10) who had improved appreciably after lobectomy started to regress about one year later into a state of severely deteriorated hebephrenia, and that the patient with chronic puerperal psychosis (No. 11) who had shown " marked improvement " regressed almost completely to her pre-operative state three months after the operation. It is doubtful whether the ultimate relapse of five out of the seven neurotic cases subjected to gyrectomy by Cameron and Prados should be taken as evidence that many conditions other than chronic deteriorated schizophrenia and puerperal psychosis could develop again in patients deprived of the bulk of their prefrontal cortex. It may be that in these five cases the small amount of cortex removed relative to the severity of the neurosis was the main factor responsible for the impermanency of the clinical improvement (compare McLardy and Meyer, in the press).

The above observations give no information as to whether such mental symptoms can appear for the first time after loss of the prefrontal regions. They therefore neither support nor contradict at least one interpretation of Freeman and Watts's (1942) thesis that " without the frontal lobes there could be no functional psychoses." Many of the foregoing facts are, however, manifestly inconsistent with such a rigid theory of relationship of structure to mental function as propounded by Kleist and doubtfully compatible with Freeman and Watts's (1948) more dynamic concept that " a neurosis or psychosis actually begins with a certain fixation of ideational activities and their underlying neural substrates in the tip of the frontal lobe," energized largely through the dorsomedial nucleus of the thalamus. The facts call for some more plastic concept of brain function such as has been advocated by Lashley (1941) and Golla (1943, 1946) : plasticity in recovery of abnormal as well as normal function.

Summary

Six patients are described in whom mental illness

recurred some considerable time after apparently successful leucotomy and in whom the precise extent of the brain lesions was subsequently determined in the laboratory. Anatomical features of the six cases are discussed, together with those of other " psychosurgical " cases in the literature in which the extent of the lesions was determinable during life. Clinical features of the six cases are reviewed together with those of other relapsed cases in the literature of " psychosurgery " in which diagnostic details are available. The following conclusions are come to :

1. Many of the symptoms and syndromes characteristic of affective and schizophrenic functional psychoses can recur after practically complete isolation of the prefrontal cortex from its long fibre connexions. Some chronic schizophrenic symptoms, at least, can not only persist but can disappear and then recur after full bilateral prefrontal lobectomy. Many neurotic symptoms can recur after disappearance following removal of more limited amounts of prefrontal cortex.

2. The illness which recurs is practically always of the same type as the pre-operative one.

3. There are indications that the power of environmental influences for both good and ill may be augmented after the operation.

4. Case 1 also touches on the problem of localization in the prefrontal regions in relation to type of personality change and to creative ability.

5. The facts demand a generous conception of the degree of plasticity within both the abnormally and the normally functioning brain.

The writers wish to express their thanks to Professor Alfred Meyer for his help throughout the preparation of the paper, to Professor Aubrey Lewis for his criticisms, to Miss M. A. Lane for her investigations of the social factors in Case 1, and to the Medical Superintendents by whose courtesy the clinical and pathological material was made available.

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OBSERVATIONS ON THE WAVE AND SPIKE COMPLEX IN THE ELECTRO-ENCEPHALOGRAM

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The classical 3-per-second waves associated with negative spikes in the electro-encephalogram (EEG) have been well-recognized findings in cases of petit mal since they were first clearly described by Gibbs, Davis, and Lennox (1935) and again by Gibbs, Gibbs, and Lennox (1937). These latter describe the wave and spike pattern in 82 per cent. of cases where there is a history of petit mal alone and in 65 per cent. of cases where there is a history of grand mal in addition. In 6 per cent. of cases of grand mal, where clinical attacks of petit mal have not been perceptible, the wave and spike pattern is also found (Gibbs, Gibbs, and Lennox, 1943). These workers found the wave and spike phenomenon in only 1 in 500 cases of 7,600 non-epileptic neurological patients and normal controls, while Williams (1944) states that the only case in 8,000 in which he observed a wave and spike outburst in a non-epileptic subject was in the identical twin of an epileptic. The association of this EEG pattern with idiopathic epilepsy, particularly the petit mal variety, therefore needs no further emphasis.

There are some general aspects of the wave and spike complexes which have received little attention, and in the present paper an attempt has been made to describe some of these features by analysing a series of a hundred records which were selected purely on the grounds that they contained outbursts of typical wave and spike formations, the clinical aspect being largely a secondary consideration. Particular attention has been paid to the general character of the records, the incidence of the complexes, and their mode of development, excitation, duration, and relationship to clinical attacks.

Method and Material

Bipolar recordings of at least fifteen to twenty minutes' duration were obtained from a 3- or 6-channel ink-writing electro-encephalograph, two rows of saline pad electrodes being placed over each hemisphere. The subjects had taken no food for three hours beforehand. They lay comfortably with eyes closed during the recordings, which were made in four positions: two antero-posterior (parasagittal and temporal) and two transverse (frontal and central, central and post-central). The effect of opening and closing the eyes was noted in all cases, and overbreathing, as suggested by Lennox, Gibbs, and Gibbs (1936), was done for two and a half to three minutes by the majority of subjects.

One hundred consecutive records showing typical wave and spike formations were examined systematically. Atypical and abortive forms were disregarded. The subjects were all known or suspect epileptics and there was an approximately even distribution between the sexes. The ages in seventy-five out of the hundred cases ranged from 5 to 20 years inclusive. Records were not usually made from children under the age of 5 years, and there were only three such in the present series. Eight of the patients were over 30 years old, the two eldest being aged 46 years.

Most of the subjects had been diagnosed clinically as suffering from simple petit mal, though some of these were also having occasional myoclonic or grand mal attacks. A small number of the subjects suffered either from grand mal alone, or attacks the nature of which was clinically somewhat doubtful.

General Characters of the Records

Before examining the wave and spike complexes themselves, the general characters of the records were first studied and compared.

In eighty-eight cases the dominant frequency in the post-central areas showed the characters and distribution of normal alpha rhythm. In fifty-seven of these, that is in just over half of the whole series, this rhythm was a prominent feature and had an amplitude of about 50 microvolts or more, whereas in only twelve cases was it irregular, ill-defined, or absent.

Apart from the wave and spike complexes, fifty-eight records were otherwise normal. Abnormal rhythms observed in the remaining forty-two cases were classified as follows:

Delta range (1–4 c/sec), often seen as 3 c/sec waves in both occipital regions	17 cases
Theta range (4–7 c/sec)	13 cases
Generalized dysrhythmia	9 cases
High voltage fast activity	6 cases

Alth ough 3-c/sec waves were noted, isolated kes were not seen in any of the records.

Special Characters of the Wave and Spike Complexes

Effect of Overbreathing.—In eighty cases typical wave and spike complexes occurred in the ordinary resting records, irrespective of whether they were produced by overbreathing. In the remaining twenty cases the wave and spike complexes were seen only as a consequence of overbreathing. Overbreathing was done by eighty-two of the hundred patients, and in no less than seventy-four of these the complexes developed apparently as a result of this procedure. They appeared either during the course of overbreathing or very shortly afterwards, the former being much the commoner. In thirty-three cases wave and spike complexes appeared during both these periods. The importance of overbreathing in precipitating wave and spike outbursts is thus very evident.

Effects of Opening and Closing the Eyes.—The effect of voluntary opening and closing the eyes several times during the recording was noted in all cases. Wave and spike complexes occasionally developed within 5 seconds or less of these movements. In eight cases they followed opening, and in fifteen cases they followed closing of the eyes. This response might be seen once or several times in a single record. In four cases wave and spike complexes on occasion followed both opening and closing of the eyes. In three cases opening of the eyes inhibited an existing wave and spike outburst.

Incidence of Outbursts.—In the standard length of record before overbreathing the number of outbursts of wave and spike complexes varied considerably from case to case. The smallest number was one and the greatest twenty-nine. In ten records there were ten or more, but the average number of spontaneous outbursts in a single record was between three and four.

Duration of Outbursts.—The duration of wave and spike outbursts was also very variable. The shortest period was less than 1 second, but the longest was almost continuous and consisted of a series of long outbursts (often of half to one minute each). In the latter case each new outburst would appear either as the preceding outburst died away or just after it had done so. The average duration of single outbursts per record was noted, and in only twenty cases did this amount to 15 seconds or more. The average for the whole series was 8 seconds.

The length of individual outbursts in a single record showed much variation, but in some cases there was a striking constancy. This applied both to the spontaneous outbursts and to those induced by overbreathing. A few examples will suffice. Thus, in one instance there were four spontaneous outbursts and two associated with overbreathing, the duration of each of them being 3 seconds. In another record there were twenty-nine spontaneous outbursts—all brief, lasting between 1 and 3 seconds each. In another instance all nine spontaneous outbursts and all six associated with overbreathing lasted approximately 2½ seconds. In another the duration of three spontaneous outbursts was 6 seconds, 6 seconds, and 5 seconds, and that of two outbursts with overbreathing 5 seconds each. In another record there were only two outbursts, each of 9 seconds, and in another only two outbursts, each of 15 seconds. In two other instances the duration of bursts was respectively 14 seconds, 14 seconds, 13 seconds, and 13 seconds, 13 seconds, 12 seconds. It thus appeared that in some cases there was a strong tendency for the length of the outbursts to be stabilized, and this applied whether the duration of each outburst was long or short.

Pattern of Outbursts.—In ninety-four cases the waves and spikes were entirely generalized, appearing in all leads. In three cases the wave and spike pattern appeared in the frontal leads only. In three other cases the discharge was seen to be both generalized and localized at different times in the same record. The localized outbursts in these cases were frontal in one instance, occipital in another, and both frontal and occipital on different occasions in the third.

In most cases the wave and spike outbursts appeared abruptly in the record although they were sometimes heralded by a short run of irregular slow waves. Usually this irregularity of rhythm began and ended synchronously in all leads, but there was a tendency for the wave and spike complex in such cases to assume its characteristic form more quickly and more clearly in the fronto-parietal leads. The wave and spike complexes also tended to persist longer in these leads, but the generalized dysrhythmia usually ended as synchronously as it began. In about 10 per cent. of cases the dysrhythmia was first and last manifest in the fronto-parietal regions, and in 5 per cent. or less it was first and last seen in the occipital leads. In the course of the longer bursts it was noticeable, as pointed out by Jasper (1941), that

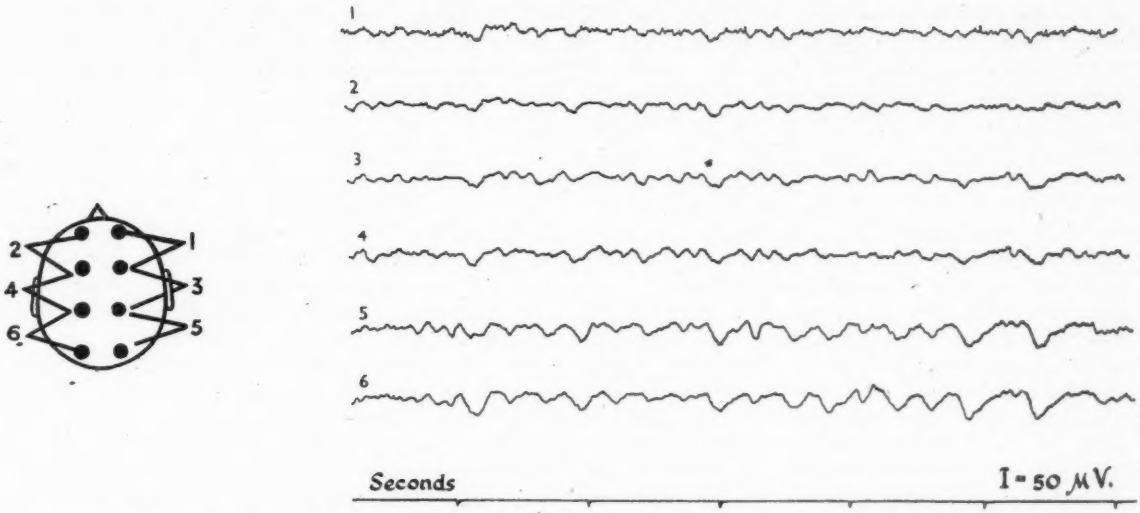

FIG. 1.—3–4 c/sec activity in the occipital regions. A single outburst of wave and spike activity was seen in this record only during overbreathing.

the wave and spike complex tended to decrease slightly in frequency, for example, from between 3 and 4 c/sec at the onset to between 2 and 3 c/sec at the end of a paroxysm. The spike component of the complex frequently appeared to become "locked" in a fixed position relative to the slow wave and both frequencies diminished together. Other small spikes or sharp waves were sometimes seen at varying points on the slow wave during the burst, and the spikes sometimes disappeared before the slow waves. The pattern of wave and spike was least characteristic in the occipital leads.

Relationship of Complexes to Clinical Attacks

Twenty-nine patients showed obvious clinical attacks of petit mal, associated always with wave and spike complexes during the recording. It was noticeable that almost all of the EEG outbursts associated with a clinical attack were considerably longer than the average duration of 8 seconds. To this there were only two clear exceptions. First, clinical petit mal sometimes occurred in association with brief, irregular, repeated bursts of wave and spike patterns during the course of overbreathing. Secondly, clinical attacks were associated in one case with brief, repetitive, spontaneous outbursts of constant duration.

In this case there were sixteen spontaneous bursts and three bursts associated with overbreathing, each of them lasting 4 to 5 seconds and each accompanied by clinical petit mal. There were no bursts of longer duration in this case, and the tendency to a fixed pattern of discharge, accompanied by a clinical attack, seemed strong. This patient was having petit mal attacks almost every day. On the other hand, fairly long outbursts of wave and spike complexes sometimes occurred without any evidence of a clinical attack being detected during the routine recording. For example, in one instance an outburst lasted over 30 seconds without any evidence of a clinical attack. No special methods were used for the detection of an attack, however, so that probably the mildest changes in consciousness were sometimes overlooked.

It was observed that, as a rule, there was little or no relationship between the frequency of petit mal attacks, as given in the patient's history, and the number of wave and spike outbursts occurring in the EEG. The liability to attacks seemed to be rather more closely related to the duration than to the number of outbursts which were found in the record. Thus, one long burst of waves and spikes was found to be more usually associated with a history of frequent clinical attacks as well as with an attack during the recording than were several short outbursts. In this series, however, no constant relationship was found between the severity of the clinical symptoms and the extent of the EEG changes.

In the present investigation we have not found any focal or other distinctive features in the records of patients having extremely frequent and brief petit mal attacks, clinically compatible with the diagnosis of pyknolepsy. Grey Walter (1938) has referred to a delta focus situated in the occipital poles in cases of so-called pyknolepsy of children

and in the present series there were eight patients whose records showed delta activity localized to the occipital regions (see Fig. 1). Clinically, however, this group showed no special features which in any way distinguished them from the remainder of the patients.

There were two patients in the series whose records showed localized wave and spike outbursts in the occipital regions. The first was a boy aged 9 years, who had been having petit mal attacks (" sometimes 7 or 8 while having dinner "), for two years ; these had first begun two months after mild concussion, but there were no abnormal clinical or radiological findings. It was of interest that his mother had suffered from fainting attacks when pregnant. The other patient was aged 10 years, had suffered from ordinary petit mal attacks for three years, and at the time of recording was having about one attack daily. These case histories were entirely comparable with those whose records showed no sort of occipital focus. Similarly, there were no special clinical features among the five cases whose records appeared to show a focus of wave and spike activity in the frontal regions.

In four cases of petit mal the EEG was recorded both before and during the administration of " tridione." In each instance wave and spike outbursts were found before treatment was begun. Three of the cases showed a satisfactory clinical response to the administration of the drug in the usual dosage of one capsule (0·3 g.) given thrice daily. In the first case wave and spike outbursts disappeared from the record, but in the second they persisted unchanged, while in the third they not only persisted but were of even longer duration than originally. The fourth case showed no clinical improvement with " tridione," although the EEG showed increased stability and at least temporary abolition of wave and spike outbursts.

Discussion

Several interesting points emerge from a study of these records, and are considered worthy of further discussion. Moreover, from the data it is possible to construct a composite picture of an " average " type of record containing wave and spike activity likely to be met with in a case of already diagnosed or suspect petit mal.

As regards the general characters of the records, it is to be noted that in rather more than half the cases these were quite normal in appearance, apart from the presence of wave and spike activity. In nearly 90 per cent. of cases there was a well-marked normal alpha rhythm which was dominant in the post-central areas, and in 57 per cent. of cases had an amplitude of 50 microvolts or more. Of the additional abnormalities observed, the commonest (seventeen out of forty-two cases) was the presence of delta activity usually occurring as bilaterally synchronous medium voltage waves at about 3 c/sec in the occipital regions. The next commonest abnormality was the presence of theta activity considered excessive in amount for the age in question (thirteen out of forty-two cases). Lastly, it may be emphasized that the occurrence of high voltage fast activity was a comparative rarity (6 per cent. of cases), while a generalized dysrhythmia containing several differing frequencies was seen in only 9 per cent. of the cases.

Overbreathing was frequently associated with the appearance of wave and spike outbursts, and the fact that in twenty cases these appeared only when the patients were made to carry out this procedure is ample testimony to its value in the confirmation of a diagnosis which may be otherwise doubtful. There is sometimes great difficulty in persuading small children to overbreathe satisfactorily, but every effort should be made to obtain their co-operation, since this procedure may yield information which cannot readily be obtained by other means.

It was notable that in nineteen of the hundred cases wave and spike outbursts seemed to be precipitated by either opening or closing the eyes, more commonly the latter (see Fig. 2). Any form of attention, visual or otherwise, is well known to abolish normal alpha rhythm, and it may be that altered visual attention or mental concentration was a factor in these cases. Since, however, these outbursts of wave and spike complexes were often quite transient and might be related either to opening or to closing of the eyes, it is possible that they were precipitated by other factors associated with the voluntary movement of the eyes or lids rather than by simple visual attention.

The figures show that there is no constant relationship between the length and number of the wave and spike outbursts in the EEG and the occurrence of a clinical attack during the recording. It is also clear that from the study of a single record one cannot estimate accurately what may be happening clinically in terms of the number of daily, weekly, or monthly attacks. In further support of this point, we may quote the case of a youth aged 21, not included in this series, who had had typical petit mal attacks regularly since the age of 10 years, and who at the time of examination was having two to five attacks daily. His EEG showed a very mild generalized abnormality of non-specific type but nothing suggestive of wave and spike activity.

These observations are in keeping with the

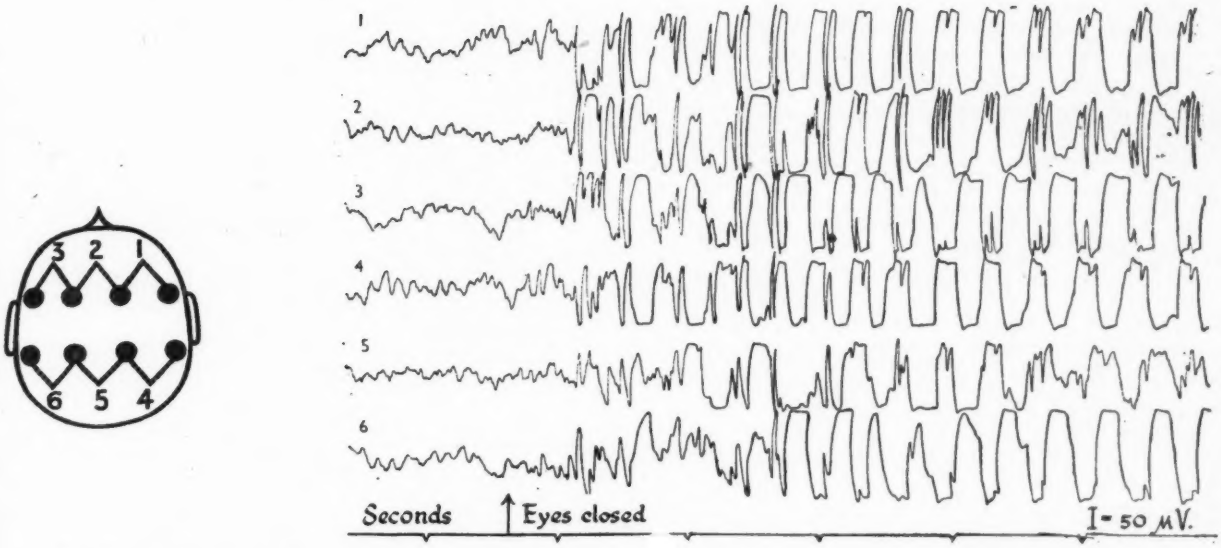

FIG. 2.—Development of wave and spike outburst immediately after closing the eyes. In this case voluntary closure of the eyes was followed on nine out of sixteen occasions by well-marked wave and spike complexes. On four of these occasions a clinical petit mal attack was observed.

suggestion of Williams (1949) that there are at least two main factors which interact in the production of clinical attacks; on the one hand there is the dysrhythmia in the EEG, and on the other hand there may be an additional hidden factor of "convulsibility," representing a liability to respond to appropriate dysrhythmia with the production of major or minor fits, as the case may be.

The fact that twenty-nine patients are noted as having had obvious clinical attacks of the petit mal variety during the recording is one which requires considerable qualification, because the clinical manifestations of these attacks are often so slight that they can easily pass unobserved when the attention of the operator is temporarily distracted from the patient, as indeed must often be the case. Fortunately this difficulty is rarely of any practical importance.

The results of the present investigation lend no support to the conception of pyknolepsy as a condition entirely independent from petit mal, since the records of the patients who had been diagnosed as suffering from the former condition showed no focal or other special features to distinguish them from the remainder. The term "pyknolepsy" (meaning crowded or condensed seizures) was first introduced by Sauer (1912). The attacks to which he applied it had been previously described by numerous writers, particularly by Fürstner (1896), who regarded them as probably hysterical in origin, and by Friedmann (1906) who called them "non-epileptic absences or short narcoleptic attacks." The first English account of pyknolepsy was given by Adie (1924) who recommended the use of the name because it was purely descriptive and non-committal. He questioned the then prevalent view that pyknolepsy was a disease *sui generis*, and subsequent opinion has more and more come to regard the condition as a form of idiopathic epilepsy. Jelliffe and Notkin (1935), in a review of the literature, concluded that most of the reasons offered by the various workers for regarding pyknolepsy as a separate entity could hardly bear criticism. More recently Owen and Berlinrood (1942) made a clinical and electroencephalographic study of eight cases of pyknolepsy. They found typical wave and spike patterns of the petit mal variety in the records of five cases, and they also noted that attacks could be precipitated by overbreathing; their conclusion was that pyknolepsy was no more than a form of petit mal epilepsy. We are in agreement with this view and there seems little to commend the retention of the term pyknolepsy as distinct from petit mal.

The number of cases treated with "tridione" in the series is too small to be of much value, except perhaps to emphasize the fact that the appearances in the EEG do not necessarily run parallel with the clinical response. They illustrate the exceptions to the general rule observed by Lennox (1947) that disappearance of clinical petit mal is usually followed by reduction or disappearance of wave and spike

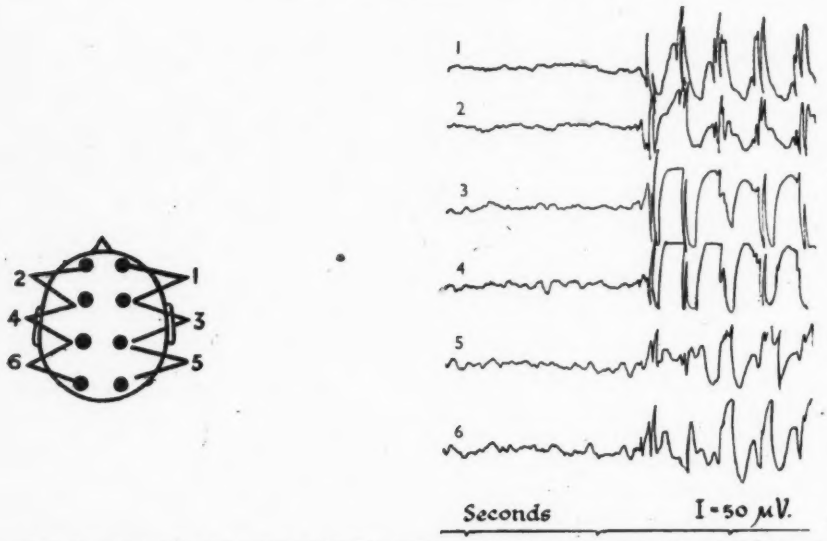

FIG. 3.—Spontaneous wave and spike outburst, showing characteristic abrupt onset.

activity in the EEG. Moreover, the observations in this small series suggest that the findings in the EEG alone cannot be taken as a reliable indicator of a favourable response to "tridione" therapy, and we cannot therefore agree with Peterman (1948) that in idiopathic epilepsy the EEG "provides the only objective evidence for a true evaluation of treatment."

Finally, taking the data as a whole, it is interesting to construct a hypothetical "average" type of wave and spike record. In the first place it is rather more likely than not to be an otherwise normal record. In eight out of ten cases the wave and spike outbursts will occur in the resting record, and in a still greater proportion they will also develop as a result of overbreathing. There will be almost a one in five chance of their being precipitated by opening or closing the eyes. In the resting record there will probably be three or four outbursts, each lasting rather less than ten seconds, and not often more than fifteen. Typically each wave and spike outburst begins fairly abruptly as a bilaterally synchronous rhythm of high voltage, in which the waves and spikes are "locked" together as recurring complexes (Fig. 3). These complexes usually assume their most characteristic form in the fronto-parietal regions. Their frequency in the initial stages is at 3.4 c/sec, but gradually slows down in the later stages to 3 and sometimes even 2 c/sec. Finally, the spikes begin to disappear and the outburst dies away in the form of a few slow waves of decreasing amplitude, ending synchronously in all areas (Fig. 4). During the recording there is perhaps about a one in three chance of there being easily detectable signs of a clinical petit mal attack.

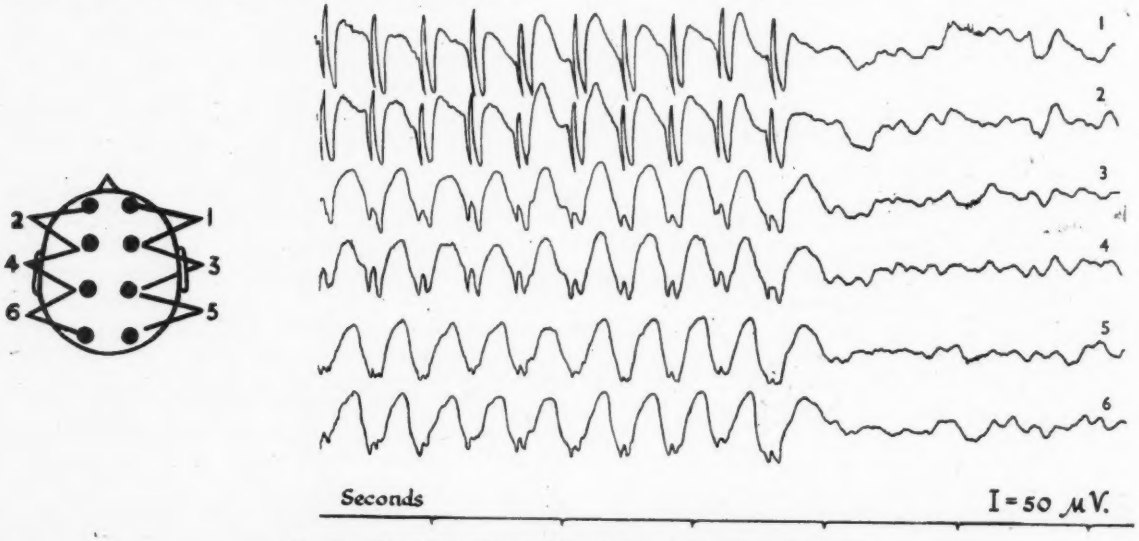

FIG. 4.—Characteristic ending of wave and spike outburst.

Summary and Conclusions

The EEGs of one hundred cases showing typical wave and spike complexes were examined. Seventy-five of the patients were aged from 5 to 20 years inclusive.

Normal alpha rhythm was seen in eighty-eight cases. Apart from the wave and spike complexes fifty-eight records were otherwise normal. Abnormal rhythms seen are described.

In eighty cases the wave and spike complexes occurred without overbreathing, but in twenty cases they appeared only when the patient overbreathed.

Overbreathing was done by eighty-two of the patients, and seventy-four of these developed wave and spike complexes in relation to the overbreathing.

The effect of opening and closing the eyes was observed in all the hundred cases. In eight cases wave and spike complexes followed opening, and in fifteen they followed closing of the eyes. In four of these cases there was a response both to opening and closing movements. In three cases opening of the eyes was seen to inhibit an existing wave and spike outburst.

The average number of wave and spike outbursts in a record before overbreathing was between three and four.

The wave and spike outburst might last for less than a second or be almost continuous for several minutes. The total average duration of a single outburst per record was 8 seconds. The length of individual outbursts in a single record showed much variation but in some cases there was a striking constancy of duration of the outbursts.

In ninety-four cases the wave and spike complexes were entirely generalized. In three cases localized as well as generalized outbursts were seen. In three cases the complexes were localized to the frontal regions only. No special clinical features distinguished the few cases in which localized outbursts occurred.

In most cases the wave and spike outbursts appeared abruptly and synchronously in all leads. The complexes themselves might be preceded and followed by a short burst of irregular waves, and there was then a tendency for the wave and spike complex to assume its characteristic form more rapidly and more clearly in the fronto-parietal regions. The wave and spike complexes tended to persist longest in the area in which they were first seen. In about 10 per cent. of cases the outburst was predominantly fronto-parietal, and in 5 per cent. or less it was predominantly occipital.

During long outbursts the wave and spike complex tended to decrease slightly in frequency.

Twenty-nine patients showed obvious clinical attacks of petit mal during the recording. All clinical attacks were associated with wave and spike outbursts, and these were usually of longer duration than the average. The liability to clinical attacks seemed to be rather more closely related to the duration than to the number of outbursts in the record, but there was no constant relationship between the severity of the clinical symptoms and the extent of the EEG changes.

So-called "pyknolepsy" could not be sharply distinguished from petit mal by the EEG any more than it could by clinical standards.

The clinical response of cases of petit mal to treatment with "tridione" was not necessarily associated with parallel changes in the EEG.

A random twenty minutes EEG record is of limited value in assessing the frequency of attacks, prognosis, or progress of a patient with petit mal. It may, however, have great diagnostic value in doubtful cases.

We wish to thank Dr. Denis Williams and Dr. W. A. Cobb for their helpful criticism in the preparation of this paper.

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PSYCHIATRIC CHANGES ASSOCIATED WITH FRIEDREICH'S ATAXIA

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The occurrence of mental changes in association with Friedreich's ataxia has received sporadic notice from time to time. Saquet (1919) reviewed the literature on this subject. Further contributions from the neuro-pathological standpoint came from Trelles (1934), whilst the genetics of this association received comment from de Smet and others (1937). Sjögren (1943) and Davies (1949) have discussed the occurrence of dementia in Friedreich's ataxia, whilst Bleuler and Walder (1946) have attempted to clarify Bleuler's concept of "the psycho-organic syndrome" by reference to the peculiar "Friedreich psychosis" which has been described by several authors, among whom we may note Klein (1937).

The aim of the present study is to describe some cases of mental change associated with Friedreich's ataxia, and to draw attention to certain clinical features of these cases, in an attempt to advance our knowledge of these curious states.

Material and Methods

Twenty cases of Friedreich's ataxia were seen. Three of these were met at the Maudsley Hospital, to which they had been admitted on account of severe mental disturbance. Many were traced through the neurological clinics of various London teaching hospitals. Certain of them were found to have become chronic inmates of London County Council hospitals. In every case the diagnosis had originally been made by a neurologist of some distinction, and frequently the patients had been seen at various times by more than one such consultant. Each case was examined physically and mentally, special enquiry being made for disturbances of thought, mood, and consciousness. Any history of fits in patients or relations was particularly sought. Various clinical tests of mental state were applied in each case, in addition to formal intelligence testing, the results of which have already been described (Davies, 1949). Electroencephalography was carried out in fifteen cases.

Case Histories

A few of the more interesting cases from the standpoint of the present investigation are described briefly here.

Case 1.—This patient, a boy of 15 years, was admitted to the Maudsley Hospital on Dec. 12, 1946, complaining of unreality feelings, hypnagogic hallucinations, transient losses of consciousness, and irritability.

Reference to the family tree (Fig. 1) shows abortive forms of Friedreich's ataxia in II/2 and III/6. II/7 is subject to recurrent attacks of depression, and III/9, the patient's mother, committed suicide in a second depressive attack.

The patient was a normal child until the age of 13 years, when scoliosis, ataxia, and titubation of the head first appeared, leading to a diagnosis of Friedreich's ataxia. He was a happy but somewhat solitary child, devoted to his father and step-mother (who was also his maternal aunt). In July 1946 he started housebreaking, then absconded from home, and on return was stubborn and irritable. In November 1946 he put poison in his father's food, and bought a rope with which to hang his step-mother. Later that month he was found wandering in a state of confusion. About this time he became strange at school where, following a retrosternal "feeling of excitement," he would suddenly bang desks and shout for a few minutes, subsequently having no recollection of this behaviour. On going to bed he would see visions

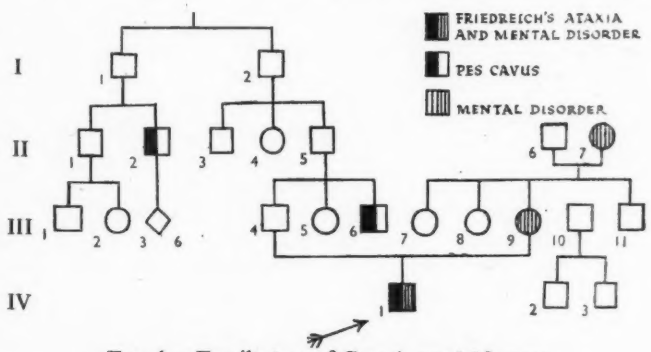

FIG. 1.—Family tree of Case 1, aged 15 years.

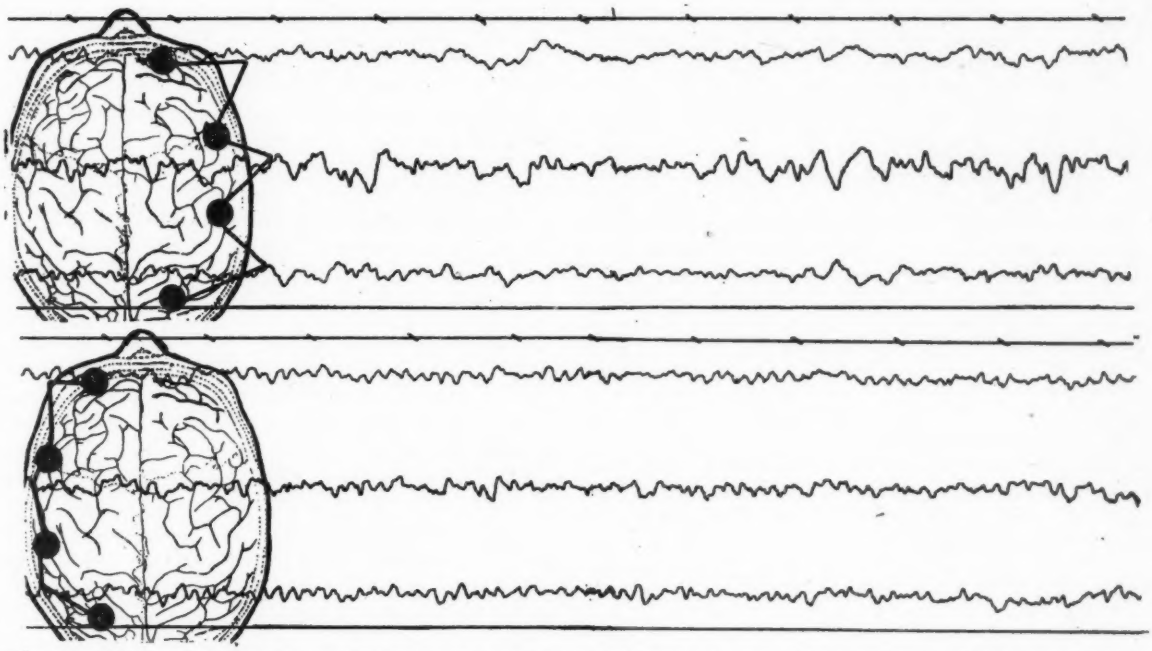

FIG. 2.—Electro-encephalogram of Case 1, showing slow frequencies in the right temporo-occipital area (upper tracing) as compared with the left temporo- occipital area (lower tracing).

before falling asleep. The first, a diminutive man in ruffles and buckled shoes would utter the word, " Transformation " ; the second man, an archer, spoke the word, " Navardo."

On admission he was grossly ataxic, and showed, among other features, dysarthria, pes cavus, scoliosis, nystagmus, absent knee jerks, and extensor plantar responses. There was a soft apical systolic heart murmur, and the electrocardiogram revealed right axis deviation. Blood, cerebrospinal fluid, and perimetry revealed nothing abnormal. He was unhappy and tearful, expressed hatred of his father and step-mother, and said they were plotting against him : if sent back to them he would murder them. Attention, concentration, and orientation were unimpaired. Memory was good except for his fugues. Psychological testing revealed average intelligence and no evidence of deficit.

During his stay in hospital he remained paranoid and subject to sudden outbursts of rage. On at least one occasion fits with tonic and clonic phases were observed. On Dec. 30, 1946, an electro-encephalogram (Fig. 2) was grossly abnormal, showing slow frequencies throughout but most prominently in the right temporo-occipital area. On March 22, 1947, he became suddenly euphoric, denied his hatred of his family, and consented to see them for the first time. This euphoria diminished towards the date of his discharge on April 30, 1947. He worked well as a laboratory technician until October 1947, when he had a fugue. He was re-admitted in November 1947, but in December 1947 he went home. He attacked his family, threw vitriol over a neighbour, and afterwards was certified.

Case 2.—A widow aged 21 years was admitted to the Maudsley Hospital on Dec. 21, 1946 because of fits. She was one of two siblings and four half-siblings, all healthy, but her mother had titubating head tremor, absent knee and ankle jerks, and extensor plantar responses.

The patient had been a healthy child and average scholar. She was a clerk until the age of 17 years, and then a shop assistant until she married at 20 years. A few months later her husband was killed in a road accident. There were no children of the marriage. She had been a cheerful woman until March 1945, when she had three major epileptic fits within three days. In the spring of 1946 she had been admitted to another hospital in status epilepticus. In August 1946 she became clumsy with her hands, stumbled often, and dysarthria began.

Her ataxia necessitated conveyance to hospital on a stretcher. She had among other signs dysarthria, nystagmus, absent knee and ankle jerks, extensor plantar responses, scoliosis, pes cavus, and wasting of the small muscles of the hands. There was no sphincter disturbance ; blood and cerebrospinal fluid were normal. She was euphoric, often laughing out loud. She answered questions well and to the point. Orientation was good. Attention and concentration were unimpaired. Her intelligence seemed low, and formal testing gave a Wechsler I.Q. of 75. In view of her history this suggested deterioration.

During her stay in hospital her mood fluctuated considerably, between marked cheerfulness and bitter weeping. At times she was querulous and resentful.

She was frequently drowsy, and had many major fits. The electro-encephalogram revealed high voltage, frontal, paroxysmal delta activity, with slow rhythms in the right temporo-occipital area. On April 3, 1947, she went home, and she died a month later in status epilepticus. No autopsy could be performed.

Case 4.—A single woman aged 24 years was admitted to the Maudsley Hospital on May 3, 1946, complaining of depression. There was no history of mental or nervous disease in her parents or their families, but a brother (two years older than the patient) had Friedreich's ataxia and was investigated in this series. The patient had been a nervous child, shy and timid during her school years. At 14 she left school in the top standard, and in that year ataxia, pes cavus, scoliosis, and other evidence of Friedreich's ataxia were noted. She had never worked in consequence, and had become reduced to an invalid chair within a few years. A year before admission she began to be irritable, "could not be bothered with anything," and had "nothing to live for." When admitted she had the usual features of Friedreich's ataxia. At the psychiatric examination she was miserable. She answered questions slowly, and frequently was on the verge of tears. She described her mood as one of extreme unhappiness; there was self reproach and remorse. Orientation, memory, attention, and concentration were unimpaired. She seemed of average intelligence, and there was no clinical evidence of deterioration. The electro-encephalogram was within normal limits.

She improved with conservative treatment and occupational therapy, gained weight, became much more cheerful, and was enabled to return home.

Case 15.—A married man aged 28 years was traced through the London Hospital, where he had been an in patient at the age of 17 years with the diagnosis of "Friedreich's ataxia and schizophrenia." There was no nervous or mental trouble in the parents or their families. The patient was one of seven children. A younger sib had had chorea in childhood, and another younger sib had been epileptic before being killed in a road accident. The patient himself had been a normal child except for epileptic fits between the ages of 2 and 5 years. Scoliosis was first observed at the age of 10 years. He went to a secondary school at 11 years, was a good scholar, and left for an engineering job at the age of 14. At the age of 17 years, 2 weeks after recovery from influenza, he suddenly became strange in his manner. He would gaze into space and seemed visually hallucinated. Then he would shout and swear at his parents. He was prevented from strangling his baby sister, became very restless, and secreted a razor. In hospital he was reported as showing the physical signs of Friedreich's ataxia and well-marked catatonia. He was transferred to a mental hospital, where he was described as being hallucinated. He heard voices calling him into the woods. He had ideas of reference, and sudden impulsive behaviour. He improved over a period of about six months, and was discharged recovered.

When seen in December 1946 he was employed as a bookkeeper. His physical state had undergone very little deterioration. There was no mental abnormality or intellectual deterioration.

Discussion

The case histories included here are of those patients with marked mental symptoms. For reasons of space it is not possible to give other case histories where psychiatric phenomena were less evident, but reference to these, where they are helpful, will be made. It is clear that a variety of mental disorders may be seen in Friedreich's ataxia, and the symptomatology of these will be discussed.

The "Friedreich Psychosis."—Under this designation several authors, notably Klein (1937) and Bleuler and Walder (1946), have described patients showing schizophreniform illnesses. Case 1 and Case 15 in our series are excellent examples of this group (although they show some atypical features such as the tendency to remit in Case 1, and the complete recovery in Case 15). Case 1 displayed very markedly the periodic outbursts of wild excitement which have been described by nearly all those who have studied these cases. Reference to Saquet's (1919) Case VI, Kalinowsky (1929), Lhermitte and others (1933), Trelles (1934), and de Smet and others (1937) leaves one in no doubt that this furious excitement is a very characteristic feature of the behaviour of these patients. Previously there has been no record of the electro-encephalograms of such patients, although the co-existence of epilepsy with the Friedreich psychosis was noted by Kroll and Terentjew (1914), Walter and Roese (1926), and Bielchowsky and others (1934). Careful observation over a long period revealed the occurrence of epileptic fits in our 15-year-old Case 1 and the electro-encephalograph record (Fig. 2) is of great interest, characterized as it is by a theta rhythm which tends to remain unilateral and right-sided. This is the rarer abnormality which Hill (1944) found among the electro-encephalograph records of psychopaths, and he associated it with "the more dramatic and severe behaviour disorders." It was well shown in one of Hill's cases who had been charged with murder (it will be recalled here that our Case 1 made more than one attempt at murder).

The genetic implications of the association between psychosis and Friedreich's ataxia have received notice, chiefly from de Smet and others (1937). It is noteworthy in our material that in the family tree of Case 1 (Fig. 1) there is strong evidence of mental instability on the maternal side of the family, and evidence of Friedreich's ataxia in forme fruste on the paternal side of the family. If anything can be concluded from this particular case it would favour a double inheritance of predisposition to physical and mental disorder, very similar to that

claimed for their case by Birkmayer and Lenz (1939).

States of Clouded Consciousness.—Cases 1 and 2 in our series illustrated very well the occurrence of confusional periods, in this instance obviously associated with clinical epilepsy and an abnormal electro-encephalogram. It is worth recalling that in his original description of the disease which now bears his name Friedreich (1863) described periodic disturbance of consciousness associated with fits, though he called the condition "hysterical." The rarity of acute episodic disturbances of consciousness in association with Friedreich's ataxia has been commented on by Bleuler and Walder (1946), and it is significant that where such occurred in our series (Cases 1 and 2) there was associated major epilepsy.

Throughout our series there has been a noteworthy occurrence of epilepsy among patients or their siblings. Cases 1, 2, and 17 in our original series of twenty cases were subject to clinical fits and had abnormal electro-encephalograms. Case 15 had a history of epilepsy in childhood, and Case 12 had a brother who had died in a mental hospital where he had been described as an epileptic idiot. This association of epilepsy and Friedreich's ataxia has received notice in the past, but in this series, which includes some cases of Friedreich's ataxia with severe mental symptoms, the relatively high incidence of epilepsy cannot escape without comment.

In the occurrence of epilepsy with Friedreich's ataxia cardiac involvement should be mentioned. Pitt (1886) first described the occurrence of cardiac disease in Friedreich's ataxia. Evans and Wright (1942) encountered a Stokes-Adams syndrome in one of these patients, and their electrocardiographic work, with the pathological studies of Russell (1946), have clearly established cardiac involvement. This is not, however, the basis of the epilepsy seen in our cases, for electrocardiograms in the epileptic patients revealed only the minor changes described by Evans and Wright, whereas Case 3 of our original series, who had an electrocardiogram showing inversion of the T wave in all leads and whose heart was considerably involved clinically, was not epileptic.

Depressive Illness.—The patient who suffered most evidently from depression was Case 4. Mood change, loss of weight, loss of appetite and sleep, with feelings of hopelessness were present. A reactive element clearly preponderated in the genesis of the state, and she responded well to general measures of treatment.

Electro-encephalograph Changes.—Of the fifteen cases examined in this way three (who had clinical epilepsy) had grossly abnormal rhythms. Three more cases had mildly abnormal rhythms, and nine cases were reported as being within normal limits. Among the six cases with various degrees of abnormality of rhythm this abnormality included temporal theta rhythm in five cases, and one record was of the rare frontal alpha. The series is too small to provide a basis for any far-reaching conclusions, but the persistence of theta rhythms may have some bearing on the excitement in the Friedreich psychosis to which attention has already been drawn.

Personality Patterns.—In a disease which becomes evident in early adolescence it is difficult to talk of changes in personality, and in chronic invalids from any cause it is easier to note the personality traits descriptively than to assign ætiologically the relative roles of factors which may be genetic, environmental, or specific to the illness. Certainly some unusual personalities were encountered among the patients seen. One of these, an intelligent woman aged 32 years, whose physical incapacity seemed only very slowly progressive, had undergone a process of violent religious conversion. She had thrown herself into evangelical and charitable work, and supported a preacher every Sunday at numerous open air meetings. Another patient had developed tremendous religious preoccupations under the influence of her mother to whom she was tied by physical incapacity. Yet another, bedridden in hospital for many years, had turned to popular psychology and mystical modes of expression.

Two of the patients showed physical and sexual immaturity with poor intelligence. One of these, a girl of 25 years, was diabetic and a petty thief. The occurrence of diabetes with Friedreich's ataxia has been noted by Schloss (1932) and Wichtl (1933); and Flatau (1908) has drawn attention to the medico-legal implications of delinquency in Friedreich's ataxia.

Although some patients showed extreme irritability, others, in contrast, showed a contentment and serenity upon which Hanhart (1923) has commented. Our Case 5, aged 27 years, affected a lordly disdain for his similarly affected sister (Case 4), whom he despised for her willingness to consult doctors. His self-satisfaction and complacency contrasted with his sister's equally evident dependency.

Conclusions

The clinical characteristics of mental change in those affected by Friedreich's ataxia have been used by Bleuler and Walder (1946) to support their view of the "psycho-organic syndrome." The evidence they quote there for observable cerebral damage in these cases is far from satisfactory, and is at variance with the negative findings of Spiller (1910), Wichtl (1933), Trelles (1934), and Hassin (1938). Sjögren's (1943) claim for a *progressive* dementia in Friedreich's ataxia, which Bleuler accepts, has been criticised

elsewhere by Davies (1949). Nevertheless the similarity between these psychotic states and some epileptic psychoses is not denied, and the occurrence of epilepsy among our series has a bearing on this point.

There can be no "simple explanation" of the genesis of any psychosis. The psychosis of Friedreich's ataxia are no exception to this rule. The unit with which we deal is not just the individual, but the individual in his environment. Genetic and development factors must be taken into consideration, as well as the innumerable influences in childhood and in adult life which play a part in the integration of personality, some being incorporated into personality structures, and others providing the immediate factors to which such resilient personality must attune itself. To draw parallels between the psychosis of different types, as between the Friedreich psychosis and the epileptic psychoses, may be of value for diagnostic purposes but helps little towards any clearer understanding of the genesis of either. Allowing for the imponderable factors already referred to as causative agents, there is still the question of the *form* of the mental disorder to be considered. It may well be that this is to be accounted for by disturbances at levels where pathological demonstration is not possible but where reflected abnormality in the electro-encephalogram may be expected.

Summary

1. Some cases of mental disturbances in association with Friedreich's ataxia have been described. These comprise the rare form of great severity, characterized by paranoid feelings and outbursts of excitement, in addition to depressive and confusional states.

2. The association with epilepsy is discussed, and abnormal electro-encephalogram findings are recorded. It is suggested that these may help to account for some features of the symptomatology in certain of these cases.

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CRAMP IN CASES OF PROLAPSED INTERVERTEBRAL DISC

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Although cramp has been mentioned as a symptom by several writers on the subject of prolapsed intervertebral discs (Bradford and Spurling, 1941 ; O'Connell, 1943 ; Lenhard, 1947) no study has hitherto been made of its exact nature, frequency, and relationships. It was not until the routine follow-up of cases of sciatica, which had been treated surgically, was begun that it was noticed that the symptom of painful cramps in the leg was fairly common in postoperative cases. This served to focus attention on the symptom, and an inquiry about it was therefore made in all cases, both before and after operation. The purpose of this paper is to record these observations, and if possible to relate the symptom to conditions found at, or produced by, the operation, and to discuss the symptom in relation to theories now held on the ætiology of muscle cramp.

Material

The observations recorded here were made in the Department of Nervous Diseases, Royal Sheffield Infirmary and Hospital, in a series of 204 cases of backache and sciatica which were thought to be due to herniation of an intervertebral disc and were subjected to operation. The patients were operated on between the years 1939 and 1946 by Mr. James Hardman, and a routine follow-up examination was carried out in 1947, at least twelve months and up to seven years after operation. The figures given below are extracted from the complete follow-up survey carried out by the writer, the results of which will be published in a later paper.

Type of Operation.—The operation performed was either a laminectomy or a hemilaminectomy, with exploration of the disc spaces between the fourth and fifth lumbar vertebræ and the lumbosacral articulation. As much prolapsed material as possible was removed, and if exploration was negative further spaces were investigated if this was thought necessary by the operating surgeon. In about two-thirds of the cases division of one or two sensory roots, either at the same segmental level as the disc or at the segment above, was made. This procedure was adopted in an attempt to be certain that pain was relieved (Walker, 1945) and to avoid further root pressure if more material should prolapse.

This procedure has since been abandoned in favour of complete curettage of the disc space. Of the 204 patients, 142 had division of one or more posterior roots, while the remaining sixty-two had no such division. The surgeon's decision whether to section the posterior root was influenced by his estimate of the completeness of the disc removal and to a lesser extent by the severity of root pain.

Type of Cramp.—In most cases the cramp came on at night while the patient was in bed. It affected the calf alone, the thigh alone, the foot alone, or combination of these. There was always associated pain, and the patient could always feel the muscle harden or, in the case of the foot, see and feel the toes being drawn down under the sole. These symptoms were always verified before a pain in the leg was called cramp.

When there had been cramp before operation, this symptom began after the onset of sciatica and never before. The most characteristic thing about the postoperative cramps was that they were very frequent immediately after operation, occurring nightly or every other night for the first few weeks, and gradually becoming less frequent so that they occurred about weekly or monthly twelve to eighteen months after operation. With a further lapse of time they became very infrequent, occurring only once every three or four months. This infrequency made observations on actual attacks of cramp difficult. None have yet been recorded as occurring more than five years after operation.

Incidence of Cramp.—Cramps occurred as a preoperative symptom in sixteen out of the 204 cases in the series (8 per cent.). It occurred after operation in fifty-two cases (26 per cent.). Of these postoperative cases, in the group of sixty-two cases not having a sensory root divided, nine (15 per cent.) developed cramps, whereas, in the 142 cases having a posterior root division, forty-three (30 per cent.) developed cramps. Thus cramps appear twice as commonly in the cases having division of sensory roots as in those not having this performed.

TABLE I

AGE AND SEX INCIDENCE OF CASES

Series	No. in series	Average age	Age of youngest	Age of eldest	Men	Women
Pre-operative cramps	16	38	20	54	15	1
Postoperative cramps	52	36	17	50	43	9
Cases without cramp	136	36	17	68	112	24
Whole series ..	204	36	17	68	170	34

Of the sixteen patients complaining of cramp before operation, ten were relieved of this symptom after operation, while in the remaining six the cramps were more frequent and severe afterwards in all but one, whose cramps persisted at about the same frequency and intensity. It has been mentioned already that the cramp in these cases tends to come on at night while the patient is in bed, thus differentiating the pain from that of intermittent claudication. A further point of difference is the age incidence, which is shown in Table I. It will be seen that the average age of the patients with cramp was approximately the same as in the whole series of sciatica cases; this suggests that vascular factors of a degenerative type play no part in the causation of the cramp.

Sex Incidence.—The sex of the patients with cramp is shown in Table I. Although pre-operative cramps were commoner in men than in women, the sex distribution in the group with cramp after operation was similar to that for the whole series (about five men to one woman); this suggests that sex has no part in the ætiology of these cramps.

TABLE II

PRECIPITATING FACTORS IN CRAMP

Precipitating factor	No. with pre-operative cramp	No. with post-operative cramp
In bed at night	7	32
While bending or kneeling ..	0	3
While sitting	2	3
Stretching leg	2	0
While standing with weight on leg	0	3
No definite cause—cramp at any time of day or night ..	5	11
Total	16	52

Precipitating Cause of Cramps.—All the patients were asked what factors brought on the cramp. The replies (Table II) showed that nocturnal cramp occurred in more than half the cases.

Factors Relieving Cramp.—The cramp passed off spontaneously in all the patients in whom it occurred pre-operatively, but could be relieved by rubbing the affected part or by pressing the foot against something firm. In the fifty-two patients in whom cramp was postoperative, changing the position of the leg was most effective and relieved cramp in fifteen cases, pressing the foot to the ground was successful in ten, and six found that rubbing the affected part gave relief. Three patients thought they could relieve cramp by taking aspirin before going to bed, and eight cases used a combination of all these methods to obtain relief. The remaining ten adopted no particular measures but allowed the cramp to pass off spontaneously.

TABLE III

MUSCLES AFFECTED BY CRAMP

Part affected	Pre-operative cases				Postoperative cases			
	No.	%	Weakness only	Weakness and wasting	No.	%	Weakness only	Weakness and wasting
Thigh ..	2	13	0	1	3	6	1	2
Thigh and calf ..	1	6	1	0	6	11	0	1
Calf ..	9	56	5	4	29	56	10	5
Calf and foot	1	6	1	0	5	10	0	0
Foot and toes	3	19	1	0	9	17	2	2
Total ..	16	100	—	—	52	100	—	—

Site of Cramp.—The muscles affected by cramp are indicated in Table III. As many observers have previously noted, the calf muscles are by far the commonest site for muscular cramps. In the sixteen pre-operative cases, wasting of the affected muscles was found in five patients, while in all except three there was definite weakness of these muscles compared with the opposite side. Fibrillation was seen in the calf in two patients only. In the fifty-two postoperative cases weakness and wasting were less frequently found in the affected muscles, there being ten patients with wasting and twenty-three with weakness. As cramps were fairly infrequent by the time of the follow-up, this observation is of doubtful significance. The distribution of the weakness and wasting is shown in Table III.

TABLE IV

RELATIONSHIP OF CRAMP TO THE LEVEL OF THE PROLAPSED DISC

Site of prolapsed disc	Cases with pre-operative cramp		Cases with post-operative cramp		Remainder of cases without cramp	
	No.	%	No.	%	No.	%
L3–L4	0	0	0	0	4	3
L4–L5	5	31	16	31	50	36
L5–S1	9	56	31	60	72	54
L4–5 and L5–S1 ..	0	0	4	8	6	5
No disc found at operation	2	13	1	2	4	3
Total	16	100	52	101	136	101

The degree of weakness and wasting of the muscles liable to develop cramp was not significantly different from that seen in cases not developing cramp either before or after operation.

Cramp and Level of Prolapsed Disc.—The relationship of cramp to the level of the prolapsed disc found at operation was also investigated. Table IV gives an analysis of the site of the prolapsed disc in the various groups. From this it will be seen that the distribution is approximately the same in all three groups, which suggests that the occurrence of cramp is independent of the level of the prolapse of the disc.

Site of Cramp and Level of Prolapsed Disc.—In Table V the relationship between the site of cramp and the level of prolapsed intervertebral disc is shown both for the group suffering from cramp before operation and the group with postoperative cramp.

As is to be expected from the fact that a prolapsed disc can affect the nerve root either of its own or of a higher segmental level according to its medial or lateral position, there is no definite correlation between the muscle affected by cramp and the level of the prolapsed disc. The type of disc found at operation, especially as regards the position of prolapsed material, was therefore investigated next.

TABLE V

RELATIONSHIP BETWEEN SITE OF CRAMP AND LEVEL OF PROLAPSED DISC

Part affected by cramp	Pre-operative cramp			Postoperative cramp			
	L4–L5	L5–S1	No disc found	L4–L5	L5–S1	L4–5 and L5–S1	No disc found
Thigh ..	1	1	0	3	0	0	0
Thigh and calf	0	1	0	1	5	0	0
Calf ..	2	6	1	8	19	2	1
Calf and foot ..	1	0	0	1	1	1	0
Foot and toes ..	1	1	1	3	6	1	0

Relationship of Cramp to Type of Disc.—The type of disc found at operation had to be discovered from the operation notes, but in some cases no particular comments about the disc were found. It was possible to divide the cases in which special comment was made into four categories according to whether the prolapsed disc appeared as a slight medial bulge, a large central prolapse, a small lateral prolapse, or a large lateral prolapse. This is obviously an arbitrary and artificial division, as the static conditions seen at operation may not represent the true state of affairs, but it was the only method possible. In Table VI the findings are compared with those obtained in the 136 cases without cramps. The findings in the cases developing cramp after operation resemble those in the general series, but in those suffering cramp before operation there was a higher proportion with large lateral prolapsed discs. These figures suggest, therefore, that cramps are more liable to develop in cases having a large lateral prolapse of the disc. As the nerve root was often stretched over the summit of the large prolapsed discs, attention was next focused on the posterior nerve root.

TABLE VI

RELATIONSHIP OF CRAMP TO TYPE OF DISC

Type of prolapsed disc	Pre-operative cramps		Post-operative cramps		Rest of series	
	No.	%	No.	%	No.	%
No evidence of prolapse ..	2	13	1	2	4	3
Slight median bulge	2	13	15	29	32	23
Large central prolapse	3	19	21	41	56	41
Small lateral prolapse	2	13	1	2	12	9
Large lateral prolapse	7	44	10	19	20	15
No mention made of disc type ..	0	0	4	8	12	9
Total ..	16	102	52	101	136	100

Cramp and the Posterior Root Section.—It was found that most of the fifty-two patients developing postoperative cramp had one or more posterior

nerve roots sectioned at operation. Thus, only nine patients (18 per cent.) did not have a root divided, while 83 per cent. did, 54 per cent. having division of one sensory root and 29 per cent. having two. Of the patients with cramp and without sensory root division, one had paraplegia before operation which persisted afterwards and at operation the roots of the cauda equina were found to be matted together, three had very laterally placed discs with the nerve root stretched over the summit of the disc, and the remaining five had nothing special recorded about the operation. It is worth noting that in only one patient out of the fifty-two developing cramp after operation was the cramp bilateral in both calves. This patient was the only one in whom the posterior root was divided on both sides. The patient who complained most bitterly of all about painful cramps in the calf had only a partial division of one posterior nerve root. (Table VII.)

TABLE VII

CRAMP AND POSTERIOR ROOT SECTION

Part affected by cramp	Roots sectioned					
	L4	L5	S1	L4 and 5	L5 and S1	None
Thigh	1	1	0	0	0	1
Thigh and calf..	1	3	1	0	0	1
Calf	3	11	2	3	3	7
Calf and foot ..	1	1	0	2	1	0
Foot and toes ..	0	3	0	3	3	0
Total ..	6 (12%)	19 (36%)	3 (6%)	8 (15%)	7 (13%)	9 (18%)

Site of Cramp and Posterior Root Section.—An attempt was made to correlate the muscle affected by cramp with the root divided. Although there was a tendency for the thigh muscles to be affected when the fourth lumbar root was divided and for the foot to be involved when the fifth lumbar and first sciatic roots were divided, there were exceptions, as might be expected from the fact that there is an overlap between the muscles and cord segments supplying them, each muscle being supplied by more than one segment and each segmental level supplying several muscles.

Relationship of Cramp to *X*-Ray Appearances.—As muscular cramps are common in patients with arthritis of the knee, hip, or spine (Pemberton, 1935), the *x*-ray appearances were studied. It was found that in the pre-operative group 44 per cent. showed no abnormality of the lumbar spine on *x*-ray examination, while 38 per cent. had slight narrowing of the disc space and none showed arthritic changes. In the postoperative group 46 per cent. showed no abnormality, while 18 per cent. had narrowing of the disc space and 12 per cent. had arthritis. Of the 136 patients who never experienced cramp, 44 per cent. showed no abnormality, 17 per cent. had narrowing of the disc space, and 14 per cent. had arthritic lipping. The radiographs in the group developing cramp after operation and in the general series were taken at the time of the follow up, when arthritic changes, if any, would be at their maximum. The fact that the *x*-ray appearances of the lumbar spine in the cases developing cramp were roughly similar in type and frequency to those of the general series suggests that arthritis had little or no part in the ætiology of these cramps, while in the pre-operative group it played no part whatever. Radiographs taken at the time were little or no different from those taken before operation, the variation being no more than in the group not developing cramp.

TABLE VIII

RELATIONSHIP OF CRAMP TO RESULT OF OPERATION IN PATIENTS WITH CRAMP BEFORE OPERATION

Series	Number in series	Good result		Bad result	
		No.	%	No.	%
Cases with cramp before operation	16	9	56	7	44
Remainder of series ..	188	120	64	68	36
Whole series ..	204	129	63	75	37

Relationship of Cramp to Results of Operation.—An investigation was made into whether patients who had cramp before operation did better or worse than those without cramp at that stage. More detailed results will be published later, and here the cases are merely divided into good and bad. The results are without significance. (Table VIII.)

TABLE IX

RELATIONSHIP OF CRAMP TO RESULTS OF OPERATION IN PATIENTS DEVELOPING CRAMP AFTER OPERATION

Cases with cramp	No.	Good result		Bad result	
		No.	%	No.	%
One or more root divided ..	43	28	65	15	35
No root divided	9	5	56	4	44
Total with cramp ..	52	33	64	19	36
Cases without cramp ..	136	87	64	49	36
Whole series	204	129	63	75	37

TABLE X

OPERATIVE PROCEDURE ON SIXTEEN PATIENTS WITH CRAMP BEFORE OPERATION

	Disc removal only	Disc removal and posterior root section	No disc found; no nerve section	Total
No. of cases with cramp before operation only	3	6	1	10
No. of cases with cramp before and after operation ..	0	5	1	6

The next point investigated was whether, in patients developing cramp after operation, the cramps occurred more commonly in the operative failures or in the successes. It will be seen that the results are approximately the same in the groups with and without cramp as compared with the whole series and therefore the appearance of cramp after operation has no prognostic significance. (Table IX.)

Persistence of Cramp after Operation.—Of the sixteen patients with cramp before the operation, only six had it afterwards, the remaining ten being free. The operative procedures carried out on these patients were as given in Table X.

Cramp and Duration of Symptoms of Prolapsed Disc.—In order to see if there was any relationship between the occurrence of cramp and the length of history before operation, the average duration of symptoms of prolapsed intervertebral disc for the various groups was compared with that of the whole series (Table XI). In the patients with cramp before operation the duration of symptoms was slightly less than in those without it, suggesting that there was no relationship. In contrast, the patients with cramp after operation had a much longer duration of symptoms before surgical treatment; this was especially so in the patients who had cramp without root section. The longer duration of symptoms suggests the possibility of more damage to nerve roots by prolapsed material, but whether this is the correct explanation is doubtful in view of the short histories in the patients with pre-operative cramp. It seems likely that the duration of stretching of nerve fibres by prolapsed material is only one factor, and possibly of less importance than the size and site of prolapse.

TABLE XI

AVERAGE DURATION OF SYMPTOMS OF PROLAPSED DISC

Series	No. in series	Average duration of symptoms before operation
Pre-operative cramps ..	16	3 yrs. 5 mths.
Postoperative cramps: with root section ..	43	4 yrs. 10 mths.
without root section ..	9	5 yrs. 9 mths.
Total	52	4 yrs. 11 mths.
Cases without cramp pre- or postoperative ..	136	3 yrs. 9 mths.
Whole series	204	4 yrs. 1 mth.

Cramp and Type of Symptoms.—All the 204 patients under review had sciatica, but there were five without any backache and eleven with slight pain in the back compared with that along the sciatic nerve distribution. Of these five without backache, two had cramps in the calf after operation. All the remaining patients had both backache and sciatica; and, although it was difficult to estimate accurately, the impression was that there was little or no relationship between severity of sciatic pain and the occurrence of cramp. It may be argued that the occurrence of cramps after operation was more dependent on the severity of pain due to nerve root involvement than on root section, and that the latter procedure happened to be done only in the patients with severe pain. The longer duration of symptoms in the patients with cramp after operation is compatible with the greater nerve involvement in these cases. Often, however, the nerve was sectioned irrespective of the severity of pain, and sometimes this was done because of the small amount of prolapsed material removed. As these cases also developed cramp, the essential cause seems to be degenerative changes in the nerve root due to section or stretching by a prolapsed disc.

Discussion

From the results of this study, it seems that cramp is more likely to occur in cases of prolapsed intervertebral disc when there is involvement of the posterior nerve roots by prolapsed material as in large lateral protrusions. That cramp can occur as a result of posterior root irritation is well known and is an explanation of their frequency in such a condition as subarachnoid hæmorrhage. Gootnick (1943) believes that the cramps seen in arthritis of the hip or knee, in weak feet, or in intrinsic inflammatory changes in nerves, such as sciatica, are clonic contractions of a muscle group due to

reflex bombardment of the myoneural junction by a stream of impulses from the neighbouring source of irritation, and he likens them to a variety of segmental visceromotor reflex, such as the abdominal rigidity in peritoneal inflammation. This theory would explain the occurrence of cramp in the pre-operative patients. In the postoperative patients the cramp seems to be related to posterior root division. Although posterior rhizotomy is an operation which has been practised for a long time for various painful conditions, no mention of the incidence of cramp after operation could be found on perusal of the literature. After division of the posterior nerve root three possible series of changes may occur : a peripheral, a central, and changes at the site of section. These will be considered in turn.

Dividing the posterior root should, theoretically, leave the dorsal root ganglion, its afferent sensory fibres, and their terminal sensory endings in muscle intact, all degeneration occurring proximal to the cut. If there are efferent autonomic fibres in the posterior root, after section it is possible that some peripheral degenerative changes may occur, affecting either the muscle fibres, the sensory endings, the myoneural junction, or the blood supply, and rendering the muscle fibres more liable to pass into spontaneous contraction. This might be transmitted to other fibres in the muscle until spasm resulted under various sets of conditions. The existence in man of sympathetic fibres in dorsal roots has not been proved, while the presence of parasympathetic fibres arising in the lateral horns of grey matter, and running to single end plates in muscle via dorsal root and ganglion (Kuré, 1931), is not universally accepted. Apart from these possibilities it is difficult to conceive how peripheral changes may occur by other known mechanisms, though their occurrence cannot be excluded. Dawson and Ladell, in a personal communication, stated that they found the cramp produced by acute salt deficiency was relieved by an intravenous injection of salt, except in a leg from which the circulation had been cut off by a pneumatic cuff. When circulatory arrest had abolished both the ankle jerk and the reflex responses to electrical stimulation, cramp no longer occurred, either during electrical stimulation or during voluntary contraction of the muscle. This suggests that an intact reflex arc is necessary for the objective and subjective phenomena of cramp to be present together. If this is true, the cramp in rhizotomy patients is dependent on intact reflex arcs in other segments of the cord. Unfortunately, there is no muscle which is innervated entirely by one segmental level of the cord, so it is not possible to prove whether such a muscle will go into cramp after division of its sensory root. The observations recorded in this paper suggest that there may be some correlation between nerve root divided and muscle affected, but there were exceptions, as was expected from the overlap between the segments and muscles innervated. Weddell (1945) has shown in the case of pain sensation in normal skin that there is a network of nerve endings arranged so that any one area of skin is supplied by several overlapping terminals derived from different areas. In muscles the nerve terminals form a much looser meshwork, so that individual neural terminals in this meshwork are isolated from each other (Feindel, Weddell, and Sinclair, 1948). The utilization of intact reflex arcs in cramp production might be possible with this anatomical arrangement, while the reduction in pattern of afferent impulses after rhizotomy might form a basis for explanation of the pain associated with these cramps, as has been postulated in the case of nerve nets and terminals subserving cutaneous pain sensation when isolated from neighbours, instead of interweaving with them as in normal skin (Weddell, Sinclair, and Feindel, 1948). The possibility that the painful element in cramp is transmitted to the cord through intact posterior roots via sympathetic afferent sensory fibres in these rhizotomy cases cannot be excluded.

The central changes would consist of degeneration of the sensory fibres as they entered the cord as far as the intercalatory neurone in the posterior horn or even to the anterior horn cell. Loss of controlling action of afferent impulses would have an effect on these neurones and might cause them to send out impulses to the muscles, resulting in their spasm. The pain of the cramp would have to utilize intact sensory fibres at other levels as described above. The posterior root degeneration could be compared with the pathological changes occurring in tabes dorsalis. In this disease, over 90 per cent. of all cases experience lightning pains and " an abrupt reflex or half-conscious ' start ' of limb muscles may accompany the ' shoot ' of the pain " (Wilson, 1940). The periodic occurrence of painful crises associated with spasm of smooth muscle also demonstrates the motor accompaniment of changes in the posterior nerve roots. It seems more likely, therefore, that the motor component of these cramps is dependent on central degenerative changes rather than hypothetical peripheral alterations.

The third factor to be considered is the change in the cut surface of the nerve root or in the cases with pre-operative cramp the site of impingement of prolapsed disc on nerve root. Granit and others (1944) showed that an " artificial synapse " could be formed in a mixed nerve either by sectioning it

or even ligating it without damaging it enough to stop normal distal conduction. This may be the mechanism of pain and cramp production in these cases, the affected nerve or the peripheral end of the sectioned posterior root acting as a short-circuiting point causing impulses to descend perhaps antidromally.

One point needing further explanation is why the cramps diminish with time. If they are due to changes in the muscle fibres or in sensory endings, are these changes reversible with the passage of time, or do other intact fibres take over their functional connexions? If the cramps are due to changes in the cord, is their gradual diminution due to completion of degenerative changes in the cut fibre and its connexions, or is it due to the time needed for other fibres and nerve endings in the cord to take over completely the functional connexions with released neurones? Such questions cannot be answered at present, and further speculation would be unprofitable. Thus, the observations made in this paper, though interesting, do not help in the elucidation of the problem of cramp. Nevertheless, if they are confirmed, they would have to be taken into account in any theory of the mechanism of cramp.

Quinine, which was suggested by Gootnick (1943) as being effective in cramp due to reflex irritation, was not tried in the present series. By the time these patients were seen the cramps had become infrequent, so that no therapy was necessary; even if quinine had been given, its efficacy would have been difficult to assess owing to the natural improvement that was taking place.

In one patient seen after this follow-up, in whom severe cramp was a prominent symptom and in whom it persisted after the response of the sciatica to conservative treatment, quinine was very effective. This patient later needed surgical treatment owing to the recurrence of sciatica.

Summary and Conclusions

1. The occurrence of cramp as a symptom in sciatica due to prolapsed intervertebral disc was studied in a series of 204 cases followed up one to seven years after operation.

2. The incidence of cramp was found to be higher after operation when, in addition to removal of the protruded disc material, a posterior nerve root has been cut.

3. The cramp occurring in these postoperative cases gradually diminished with time.

4. The significance of these findings is discussed in relation to the mechanism of cramp production.

5. The occurrence of cramp, whether before or after operation, is of no prognostic significance as regards the operative result.

6. While not helping in elucidating the mechanism of cramp, these findings, if confirmed, must be taken into account in any comprehensive theory of cramp.

My thanks are due to Mr. James Hardman, F.R.C.S., without whose work and original suggestion, this investigation would not have been undertaken.

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BOOK REVIEWS

Observations on the Pathology of Hydrocephalus. By Dorothy S. Russell. 1949. M.R.C. Special Report. Series No. 265. London, H.M. Stationery Office. Pp. 138. Price 6*s*. net.

This monograph is the result of seventeen years of post-mortem study of hydrocephalus in the child and the adult. There are three possible causes for hydrocephalus: (1) excessive formation of the cerebrospinal fluid; (2) interference with the circulation of the fluid; and (3) failure of adequate absorption of fluid into the blood and lymph channels. Recent work discounts the first possibility, as it seems unlikely that either hypertrophy of the choroid plexuses or increased capillary pressure in them, for example, as a result of thrombosis of their efferent veins, ever result in hydrocephalus. About the third possible cause there is no certain knowledge, but a number of clinical cases of dilatation of the ventricles, as a sequel to extensive sinus throm-

bosis, usually affecting the superior longitudinal sinus, has been recorded, and the name " otitic hydrocephalus " may correctly be applied to some of these. In such cases the hydrocephalus is usually slight or moderate and subsides with the recanalization of the thrombosed sinus.

In the great majority of cases therefore, hydrocephalus is caused by obstruction to the circulation of the fluid. The three main causes of this are : (1) malformations, either at the level of the aqueduct of Sylvius or at the outlets from the fourth ventricle ; (2) meningeal adhesions, due to pre-existing inflammations ; and (3) tumours.

The malformations of the iter of Sylvius include stenosis, forking (often described as atresia as the resulting canals are of microscopic size), and neuroglial septa which usually occur at the caudal end of the canal. These maldevelopments are distinguished from post-natal stenosis by the absence of periaqueductal gliosis. Stenosis due to gliosis is considered by the author to be most probably of inflammatory origin. In some cases it may not easily be distinguished from tumour formation.

Malformations at the outlet from the fourth ventricle, such as absence of the foramina of Magendie or of Luschka or the Arnold-Chiari malformation, or deformities of the base of the skull and foramen magnum such as occur in platybasia and achondroplasia, may also result in hydrocephalus.

Meningitis may be difficult to establish as a cause of hydrocephalus in some cases, especially those beginning soon after birth, as *B. coli* and some other Gram-negative bacilli may cause transient attacks of meningeal inflammation with little clinical evidence of the disease. Meningococcal meningitis has always been a common cause of hydrocephalus, some cases having a latent period of many years before symptoms of hydrocephalus appear.

Syphilis is a much rarer cause of meningitis in children than the authors of the pre-Wassermann era considered, but a number of cases has been recorded in adults.

Tumours of very varied site and character may cause hydrocephalus and are its most common cause in older children and adults. In addition to tumours in the posterior fossa, tumours and colloid cysts in the third ventricle may cause dilatation of the lateral ventricles ; and diffuse meningeal tumours, such as metastatic carcinomas, may cause generalized hydrocephalus.

The author omits the difficult question of post-traumatic hydrocephalus, but in all other respects the monograph appears remarkably complete. It is profusely illustrated with excellent photographs and photomicrographs and its objective character and the full documentation of cases contribute to its authoritative character.

Untersuchungen aus dem Grenzgebiet zwischen Psychopathologie und Endokrinologie. By M. Bleuler. 1948. *Arch. Psychiat. Nervenkrank.* **118–180**, vereinigt mit *Z. ges. Neurol. Psychiat.*, **180**, 271–528.

A single issue of the *Archiv. für Psychiatrie und Nervenkrankheiten*, now united with the *Zeitschrift f. d. ges. Neurologie u. Psychiatrie*, is entirely devoted to a large and comprehensive study by Professor Bleuler and his assistants at Burghölzli. The aim of this work was, by working on sub-groups of schizophrenics showing a characteristic endocrine disorder, to discover whether endocrine factors play any definable pathogenetic or pathoplastic role in schizophrenia and psychopathy. The work done is of painstaking thoroughness, and the results achieved, both in their positive and negative aspects, are encouraging.

The positive results were obtained with the acromegaloid constitutional type. There are three studies on this theme, one of them, by Professor Bleuler, being an interesting pathography of Voltaire. The two clinical studies show that the acromegaloid constitutional type, which can be safely distinguished from acromegaly itself, is a largely genetically determined trait, and runs a dominant course through the families studied. It is associated with anomalies of character of a particular stamp, involving tendencies to sudden variations of mood independently of any environmental cause, and to dipsomania, poriomania, and periodic bulimia. These traits are regarded as a mid-brain syndrome. Furthermore the acromegaloid relatives of the acromegaloid schizophrenics were themselves more often schizophrenic than might be expected, and the acromegaloid constitution apparently aided the appearance of a schizophrenia. The schizophrenia so developed did not conform to the pattern of a control schizophrenic material, previously intensively studied by Bleuler (" Krankheitsverlauf, Persönlichkeit und Verwandschaft Schizophrener und ihre genenseitigen Beziehungen," Thieme, Leipzig, 1941). The psychosis tended to take a chronic and insidious but mild form, and to lead only to the less severe forms of defect.

Other familial and clinical studies are of schizophrenia, psychopathy, or psychosis associated with Cushing's disease, with virilism in women, with excessive obesity, with infantilism, and with Simmond's disease. Here there was no suggestion of any genetic or causative connexion between the endocrinopathy and schizophrenia. Several of these anomalies, such as virilism and infantilism, were shown to have a genetical basis, tending as a rule to dominance, and in the case of infantilism there was an association with oligophrenia. Nor were pathoplastic effects on the symptomatology of the schizophrenias lacking.

This work is of considerable interest, and is a further step towards the resolution of the schizophrenias into separate and recognizable clinical entities. But it is clear that we have as yet proceeded only a little way on this path.

Psychological Medicine : A Short Introduction to Psychiatry. By Desmond Curran and Eric Guttmann 1949. Third Edition. Edinburgh : E. and S. Livingstone, Ltd. Pp. viii+252. Illustrated. Price 12*s.* 6*d.*

The third edition of this excellent short introduction shows no major changes over the second. A good deal of revision has, however, been carried out, and the book has been kept up-to-date. Larger changes might have been made but for the tragically early death of Eric Guttmann. The book still remains something of a compromise between the views of the two authors, which were derived from very different backgrounds of teaching. Nevertheless it remains a singularly clear statement of basic ideas and facts in psychiatry, not tied down to any school, and clinically oriented throughout.

J. Neurol. Neurosurg. Psychiat., 1949, **12**, 259.

THE RECORDING OF NERVE ACTION POTENTIALS THROUGH SKIN IN MAN

BY

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Introduction

Electrical stimulation of peripheral nerve in man has been shown to produce cerebral responses (Dawson, 1947), and analysis of these responses has made clear the need for some means of investigating the nature of the sensory afferent volleys concerned. Experiments carried out in 1945 suggested that it was sometimes possible to record through the skin action potentials in the ulnar nerve of one of us (G.D.D.) when the nerve was stimulated electrically at the wrist. These observations were later repeated independently for the median nerve by Dr. Merton, but on both occasions the action potentials were small and could not be applied to the problems in hand; the experiments were therefore not carried further. However it later seemed worth while to repeat these experiments to see if better results could be obtained. The only previous reports of the possibility of recording through skin nerve action potentials in man which have been found are those of Rusinov and Chugunov (1939, 1940) and Rusinov (1943, 1947). They report recording nerve action potentials from over the median and ulnar nerves above the elbow when they stimulated proprioceptive sensory endings by hanging weights on the fingers, and when they pricked the hand or brushed the skin of the fingers. We have repeated the experiments of these authors with tactile and painful stimuli, but we have been unable to obtain any records resembling theirs so long as the muscles near to the recording electrodes were well relaxed. We have not repeated the experiments in which muscles were stretched, as it is difficult to avoid contraction of muscles with the stimuli they used: up to 500 g. hung on one finger. They do not seem to have carried out adequate control experiments to exclude the possibility that they were recording muscle action potentials. From the experiments to be described it now seems clear that, after electrical stimulation at the wrist, action potentials of useful size may be recorded from the skin over the more superficial parts of the median and ulnar nerves near the elbow. Since it is not generally known that this is the case, and since the technique appears to have application to the study of peripheral nerve injury and disease, it is the purpose of this paper to report the methods used and to describe the characters of the action potentials which may be recorded.

Methods

The course above the elbow of the superficial part of the median or ulnar nerve to be examined was plotted, using an electrical stimulus, and was marked on the skin. A pad electrode 1·5 cm. in diameter on a handle was used as a cathode to search for the places at which the nerve was most easily stimulated, and the stimulator anode was attached to a plate electrode 3·5 cm. by 6 cm. placed in any convenient position on the arm. To reduce the spread of the stimulus, and to give more precise location of the nerve, a small shock was used, just great enough to cause visible twitching of the forearm and hand muscles. The length of nerve which was relatively superficial varied considerably from one subject to another. Sometimes a length of more than 6 cm. was found over which the threshold for stimulation altered little; sometimes the length was less than 3 cm. In the same way the most superficial part of the nerve was plotted at the wrist. The skin over the nerve trunk was then rubbed with Cambridge electrode jelly to produce an erythema and afterwards washed with soap and water. This is important, as the production of an erythema reduces the skin resistance and the trouble from stimulus escape, but this gain may be lost if an excess of electrode jelly is left on the arm. The recording electrodes, with a small quantity of electrode jelly on each, were then applied to the skin over the nerve above the elbow and the stimulating electrodes at the wrist. In order to obtain good results the inter-electrode resistance, measured with direct current at not more then 1 volt, should be less than 10,000 ohms, but it is advisable not to prick or abrade the skin under the stimulating electrodes in order to reduce the resistance, as this may make the stimulus painful at the site of stimulation and prevent muscular relaxation. Records free from muscle action potentials were obtained only when the muscles near to the recording electrodes were relaxed. For the same reason the stimulus was always

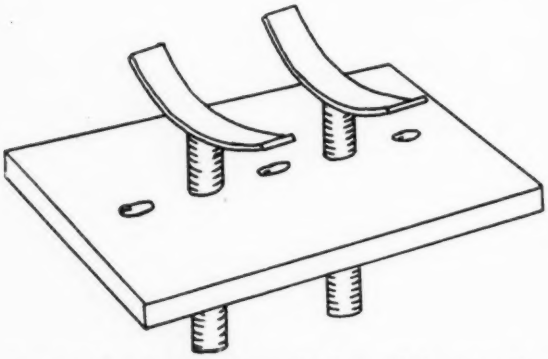

FIG. 1.—The diagram shows the form of the recording electrodes before padding with lint. The distance between the holes in the bakelite supporting block is 1 cm. Blocks of different lengths were used for different numbers of electrodes.

applied at the wrist and the record made from over the nerve above the elbow. In this way the only muscles excited by the shock were those in the hand, which were as far as possible from the recording electrodes.

The recording electrodes which were used were of the form shown in Fig. 1, narrow rectangles of silver sheet 1 mm. thick, 0·5 cm. wide, 2·5 cm. long, and curved in their long axes to locate the nerve under them. They were mounted at their centres on threaded silver tubes and covered with lint and gauze pads soaked in brine. The silver tube stems were screwed into a bakelite block in which there was a line of holes at intervals of 1 cm.; for recording nerve action potentials two or three electrodes were used at intervals of 3 cm. in a block longer than that shown in Fig. 1. The electrodes were arranged with their long axes parallel, and the blocks were pressed on to the skin by rubber or webbing straps with the length of the electrodes as nearly as possible at right angles across the course of the nerve. The form of the electrodes is important as they must be small in the direction along the length of the nerve if the site of pick-up is to be even approximately known. The effect of movement of the electrodes in a direction across the length of the nerve is minimized if they are made large in this direction; a movement of a small circular electrode away from the nerve by only a centimetre may lose the action potentials. For recording action potentials in the thenar or hypothenar muscles, surface electrodes were used, placed over the bellies of the muscles. The electrodes were either of the strip form used for recording the nerve action potentials, or were silver cups, 1 cm. in diameter, held on with collodion.

Several arrangements of stimulating electrodes have been used. In early experiments a large anode was placed on the hand or arm and for the cathode a small pad electrode was placed over the nerve; the electrodes were of the same type as those used for plotting the course of the nerve. Later it was found that the stimulus escape could be greatly reduced if both electrodes were made small and of equal size and were placed close together. When only the nerve action potentials proximal to the point of stimulation were being recorded, a pair of electrodes of the same type as those shown in Fig. 1, with the more proximal one the cathode and the more distal one the anode, was found to be suitable. However, this arrangement of the stimulating electrodes, with the anode over the nerve distal to the cathode, may lead to blocking of some of the fibres conducting impulses to the periphery, and the volleys travelling away from the electrodes in the two directions will not be comparable. To avoid this difficulty, when action potentials in muscles distal to the point of stimulation were being recorded, as well as nerve action potentials proximal to it, small silver cup electrodes were used. One of these over the nerve was made the cathode; and the other, placed several centimetres medially or laterally, was made the anode. The stimulating voltage used had a steep front rising to its peak in not more than 4 μ sec., and an exponential delay, usually with a time constant of 50 μ sec. The stimulating electrodes were both unearthed and were coupled to the stimulator through a Muirhead Wide-Range transformer. When working between input and output circuits of 2,000 ohms impedance this transformer has a flat frequency response up to 150 kilocycles per second. Since the stimulator has a low output impedance the form of the stimulating current in the tissues did not follow the form of the potential difference between the stimulating electrodes. However, the results obtained with this stimulator were consistent, and it has been pointed out (Walter and Ritchie, 1945) that a stimulator with a low output impedance tends to produce less discomfort at the site of the stimulating electrode, for any given degree of nerve stimulation, than one of high output impedance, and for this reason the low impedance type was preferred. This is important not only when examining patients but also when doing laboratory experiments on volunteers, since the subject must be as relaxed and comfortable as possible if the records are to be free from muscle action potentials. Occasionally when a search was being made for action potentials from fibres with higher thresholds a shock of the same form but with a time constant of 0·4 msec. was used.

The recording amplifiers, which have balanced input circuits, were used without grid resistances in the input stages. An earth connexion was made to the subject's forearm, between the electrodes used for stimulating and those used for recording the nerve action potentials. Differences in the contact resistance at the recording electrodes may produce a serious imbalance in the input circuits if grid resistors are used, much greater than the imbalance of the amplifiers themselves. This imbalance may increase seriously the stimulus artefact in the records, and it is easier to reduce this effect if the grid resistors are omitted. The frequency response of the amplifiers was set to be uniform within 10 per cent. from 20 c/s. to 700 c/s., and to attentuate by half frequencies of 5 c/s. and 2,800 c/s. The response of one amplifier and recorder to a rectangular pulse with a duration of 2 msec. and an amplitude of 20 μV., from a source of 500 ohms impedance, is shown in Fig. 2c. Fifty records were superimposed, and the peak-to-peak amplitude of the inherent irregularity of the apparatus (" noise ") is about 4 μV. The output of the amplifiers

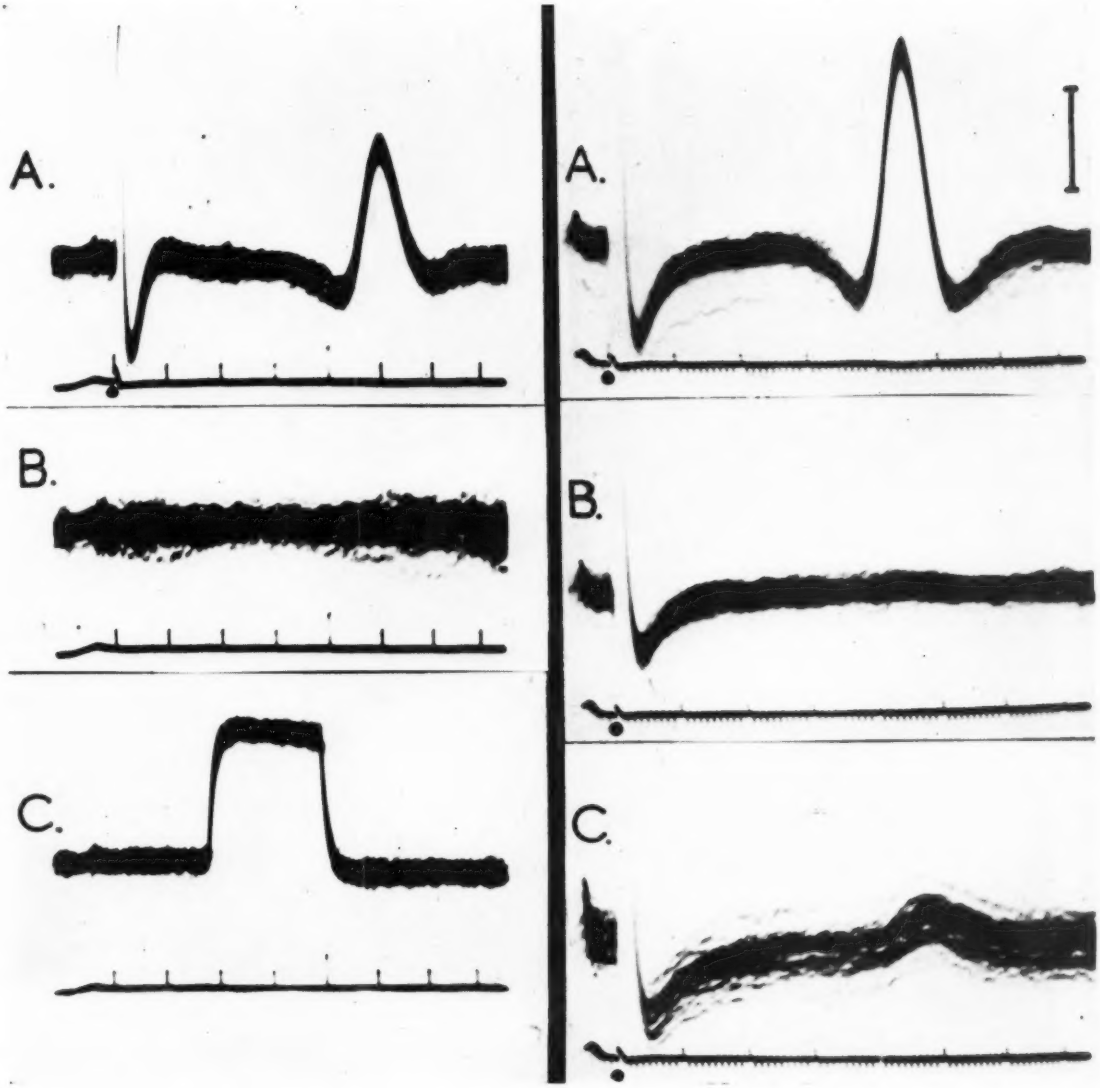

FIG. 2 (A, B, C, left).—The records show the potential differences between a pair of electrodes on the skin over the median nerve above the elbow. In (A) electrical stimuli were applied to the nerve at the wrist at the point indicated by the black dot below the time scale. In (B) the conditions were identical except that no stimuli were applied. Record (C) shows the response of the recording system to a rectangular pulse of 20 μV. amplitude delivered from a source of 500 ohms impedance. The time scales show intervals of 1 msec. In these and in all succeeding records fifty traces were superimposed.

FIG. 3 (A, B, C, right).—The records show the effects of movements of the stimulating or recording electrodes. Record (A) shows the responses recorded when the stimulating cathode was over the median nerve at the wrist and the recording electrodes over the nerve above the elbow. (B) shows the result of moving the stimulating cathode from over the nerve to the radial styloid, keeping the other conditions as in (A). (C) shows the result of leaving the cathode over the nerve at the wrist but moving the recording electrodes medially off the nerve on to the belly of the biceps muscle. The time scales show 0·1 and 1 msec. intervals.

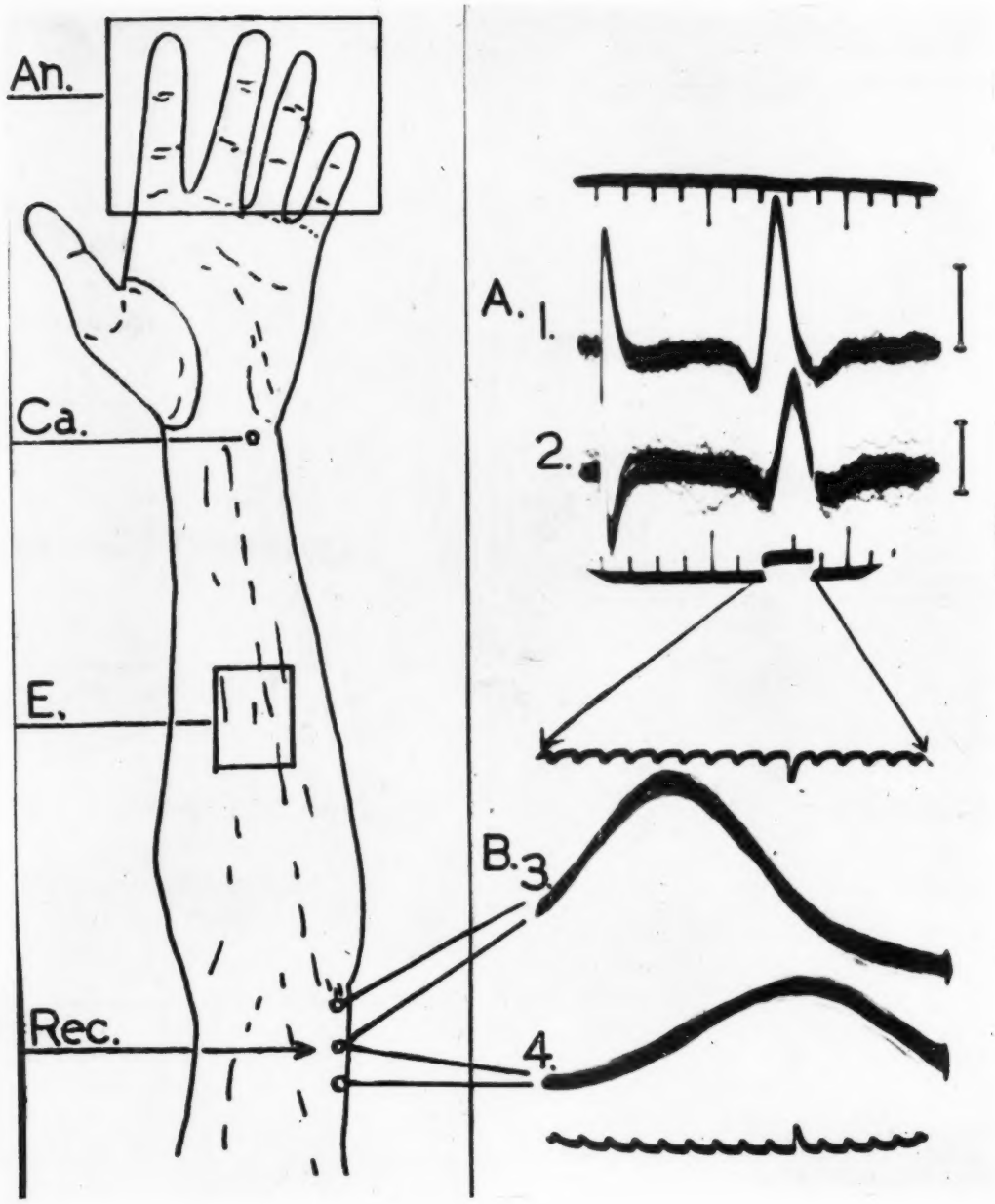

FIG. 4.—The records show the change in the latency of the responses with change in distance from the stimulating point. Traces 1 and 3 were recorded simultaneously from the distal and central electrodes, traces 2 and 4 from the central and proximal ones. The response from the proximal pair of electrodes is delayed by 0·5 msec. In the diagram the letters indicate: An., anode and Ca., cathode of the stimulator, E, earth connexion, Rec., recording electrodes separated by 3 cm. The time scales in (A) show interv. ls of 1 and 5 msec. and in (B) of 0·1 msec. The calibration marks in (A) indicate 20 μV.

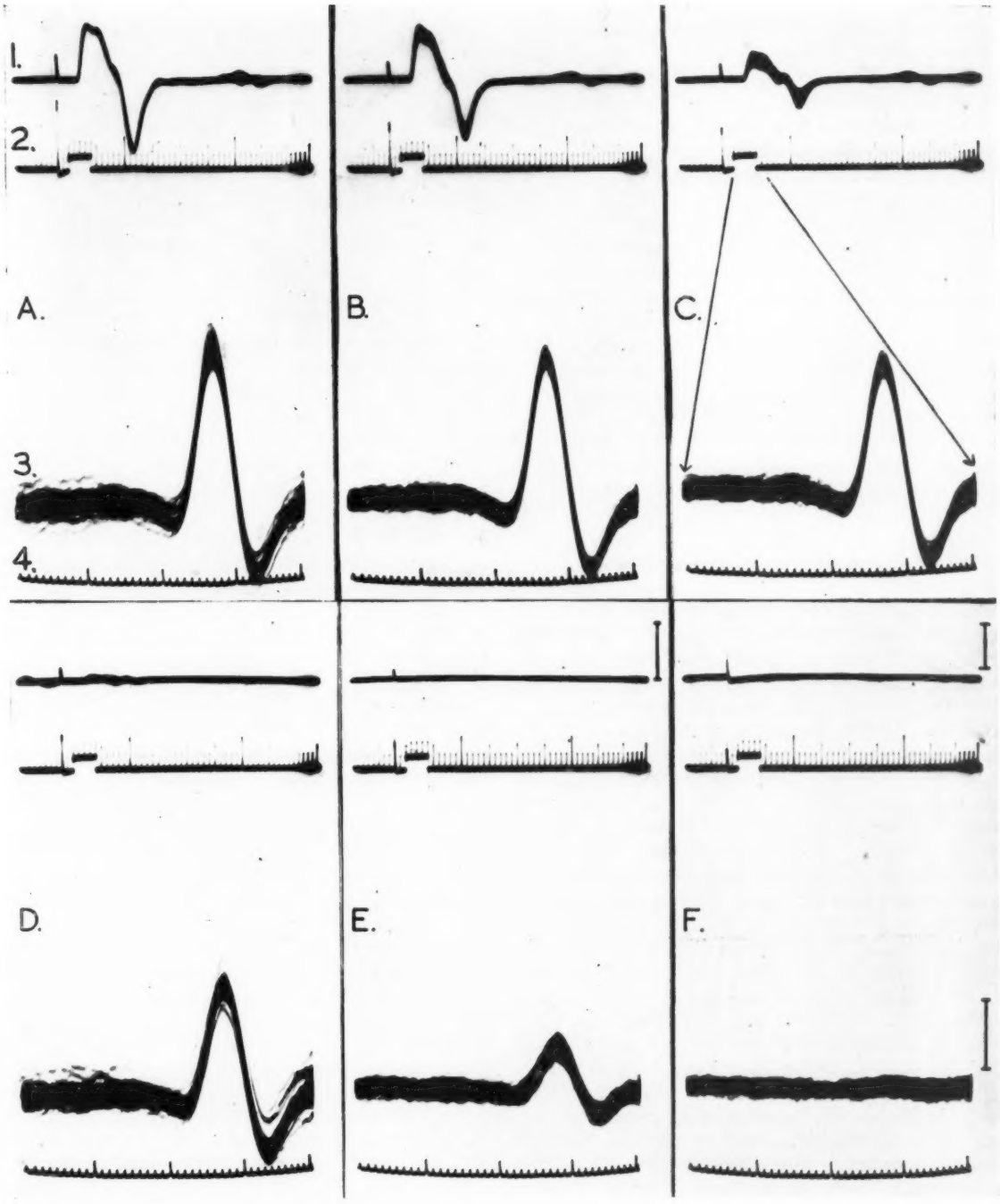

FIG. 5.—The records show the relation between the action potential volley in the median nerve and the number of motor fibres being stimulated. In trace 1 are recorded the action potentials of the muscles in the thenar eminence, and in trace 3 the action potentials from the median nerve above the elbow. In (A) the stimulus to the nerve at the wrist was supramaximal for the motor fibres, and in (B), (C), (D), (E), and (F), the strength of the stimulus was progressively reduced. Records (D) and (E) show that the greater part of the nerve action potential in (A) is due to fibres with a lower threshold than motor fibres. Trace 2 shows the time scale for trace 1 in 1, 5, and 20 msec. intervals, and the pedestal shows the relative time and duration of trace 3, the time scale for which is shown in intervals of 0·1 and 1 msec. in trace 4. The calibration mark in (E) at the end of trace 1 shows 8mV. for records (A) to (E), and that in (F) 400 μV. The mark at the end of trace 3 in (F) shows 20 μV. for this trace in all the records.

was taken to cathode ray tubes from which photographic records were made of either single responses or up to fifty responses superimposed.

Using the methods described, fifteen subjects have been examined. Of these subjects, thirteen could give no history of any neurological disorder; in the fourteenth the ulnar nerve on one side had been completely severed above the elbow and had been sutured, with good recovery of function. On the same side as the ulnar nerve which had been cut, the median nerve also had been damaged by a tourniquet at the operation for suture, but had recovered in three months. Otherwise this subject also was healthy, and in this paper only records from the uninjured side will be considered. In the fifteenth subject no history of neurological disorder was obtained before the examination, but the results in his case were so different from those in the other subjects, which were uniform, that a further inquiry was made. This disclosed a history of mild disorder which will be discussed later.

Results

Fig. 2A shows an oscillogram in which are superimposed fifty records of the changes of potential at electrodes on the skin above the elbow, produced by stimulation of the median nerve at the wrist. The stimuli were applied at the rate of one per second and were strong enough to give approximately maximal stimulation of the motor nerve fibres to the small muscles of the hand. On the lower trace in the record are shown time intervals of 1 msec., and the instant at which the stimulus was applied is indicated by the black dot below this trace. Synchronously with the stimulus the shock artefact appears in the upper trace, which was recorded from the electrodes above the elbow. This artefact lasts for 1·5 to 2 msec. and with any one electrode arrangement its size is proportional to the stimulus strength, but it may vary greatly in size, duration, and form from one experiment to the next and with the electrode contact resistance or position. With the precautions described the artefact could usually be reduced to such an extent that the baseline became flat again within 2 msec. of the stimulus, even when this was of fifty volts or more and when the record was being made with a sensitivity of 1 mm. deflection per microvolt between the recording electrodes. Next there is a triphasic wave which begins 3 to 4 msec. after the stimulus and which is complete in a further 3 msec. When the stimulus was increased slowly from zero the stimulus artefact appeared first, then at a threshold level, which was accurately repeatable, the triphasic wave appeared. This wave grew rapidly up to a point where an increase of stimulus strength of 20 or 30 per cent. produced no significant increase in its size, although the stimulus artefact continued to get larger. The stimulus strength at which the wave first ceased to increase was approximately that which gave maximal stimulation of the motor fibres in the nerve. The example in Fig. 2A is typical of the records which were obtained from over the median or ulnar nerves of fourteen subjects, though the relative sizes of the three phases of the wave varied from subject to subject. Records from the fifteenth subject at first showed no similar deflections at all, apart from the usual stimulus artefact. At a later examination, and after the courses of the nerves had been plotted with particular care, regular deflections were detected in the records between 4 and 10 msec. after the stimuli. When stimulating the median nerve on the right or left side these deflections were only just detectable above the irregularities in the records, and when stimulating the ulnar nerves they were less than half the size of the deflections in any of the other fourteen subjects. The small size of the responses and the limited area over which they could be detected probably accounts for the failure to record them at the first examination. In the other fourteen subjects the responses were recorded without difficulty at the first examination. The sizes of the responses were measured from the centre of the darkest part of the baseline in the superimposed record to the centre of the darkest part of the trace at the peak of the upward deflection, when the potential difference between the electrodes was greatest. The measurements were all made from records taken with a standard inter-electrode distance of 3 cm. and with a stimulus which was maximal to the extent that a 20 per cent. increase in its size would produce no significant increase in the size of the response. The Table gives the number of subjects in whom the sizes of the responses fell into the ranges shown, when they were recorded under the conditions described.

The connexion of the amplifiers to the electrodes over the nerve was such that an upward deflection was recorded when the more distal electrode of a pair became negative with respect to the more proximal one. The deflections between 3 and 7 msec. after the stimuli in the records in Fig. 2A, therefore, show that the distal electrode became first positive, then negative, and then positive again with respect to the proximal one. This triphasic form appeared constantly when the electrodes were at places where the nerve could be stimulated equally easily, and where it was probably equally superficial. Occasionally, when a pair of electrodes over the median nerve was more distal than usual, a predominantly diphasic wave was

TABLE

RANGE OF SIZES OF RESPONSES RECORDED

No. of Subjects	Amplitude of responses : microvolts
1	less than 10
1	from 10 to less than 20
5	from 20 to less than 30
2	from 30 to less than 40
3	from 40 to less than 50
3	from 50 up to 60
0	more than 60

recorded. This may have been due to the distal electrode being over the nerve where it was becoming less superficial as it entered the antecubital fossa. In these circumstances a typical triphasic wave was still recorded from a pair of electrodes farther up the arm. Before it may be accepted that these or similar changes are due to nerve action potentials certain sources of artefact must be excluded.

From the fifty superimposed records in Fig. 2A it seems that the triphasic wave follows each stimulus by an interval which varies by not more than plus or minus 0·1 msec. Disturbances not related to the stimulus, such as action potentials associated with steady or random contractions of muscles near to the recording electrodes, produce only irregular deflections at different parts of the trace. In Fig. 2B are shown fifty superimposed records made from the same electrodes and under the same conditions as the records in Fig. 2A, except that no stimulus was applied to the nerve. No deflections appear like those in the records in Fig. 2A. This suggests that the disturbance was provoked by the stimulus and that the time at which it occurred was accurately related to the time of the stimulus. The records in Fig. 3 show the effects of movements of the stimulating or recording electrodes away from the nerve. Fig. 3A shows the responses recorded when the stimulating cathode was over the median nerve at the wrist and the recording electrodes were over the nerve above the elbow. In Fig. 3B the records show the result of moving the stimulating cathode away from the nerve to a point over the styloid process of the radius. The stimulus artefact in the record was almost unaltered but the later deflections disappeared completely. This suggests that these later deflections were not due to spread of the stimulating current, or to any of its effects on tissues other than the nerve. When the stimulus was applied to the nerve, the small muscles of the hand which were innervated by the particular nerve being stimulated, twitched with each stimulus and their action potentials were about 8 mV. in amplitude from the baseline to the first peak. The latency between a stimulus to the median nerve at the wrist and the beginning of the action potentials in the thenar muscles was between 4 and 5 msec., which was very similar to the latency between the stimulus and the beginning of the response at the electrodes above the elbow. The disturbance above the elbow, which was never more than 60 μV. in size, might therefore have been an electrical spread of the action potentials from the twitching muscles in the hand. If the recording electrodes were moved away from the nerve, on to the belly of the biceps muscle, the size of the recorded deflections was reduced or they were abolished. The records in Fig. 3C show this effect. There is greater irregularity in the baseline because of incomplete relaxation of the biceps muscle, and the deflections 4 msec. after the stimulus are much smaller than in the records in Fig. 3A. They were probably not abolished in this experiment because the recording electrodes were of the rectangular strip type and to abolish the deflections it was necessary to move them two and a half to three times as far from the nerve as when circular electrodes, 1 cm. in diameter, were used.

The type of experiment described showed that the potential changes were greatest over the plotted course of the nerve ; if they were due to electrical conduction of the action potentials from the hand muscles there was no reason why this should have been so. In addition the action potentials from the thenar muscles were some five times longer in duration than the potential changes recorded from the electrodes above the elbow. The reduction in size of the response as the electrodes were moved away from the nerve and on to the biceps muscle also suggests that it was not due to a reflex twitch of the biceps muscle caused by the shock, and this is supported by the short latency of only 3 to 4 msec. between the stimulus and the response. Additional and confirmatory evidence that the disturbance was being conducted in nerve was found in measurements of the latency of the response at different distances from the stimulating electrodes. Fig. 4 shows two records made simultaneously from three electrodes at intervals of 3 cm. with the arrangement indicated in the diagram. In Fig. 4 the response from the distal electrode and the central one, traces 1 and 3, occurred earlier than that from the central electrode and the proximal one, traces 2 and 4. The latencies of the negative peaks of the waves differed by 0·5 msec. This is

shown in Fig. 4B, where these peaks were displayed on an expanded time scale the duration of which corresponded to the pedestal in the lower time scale in Fig. 4A. There may be considerable errors in estimations of conduction velocity made from records of this type, where the sizes of the two waves are not identical, but a time of 0·5 msec. for a conduction distance of 3 cm. would indicate a conduction velocity of the same order as that in motor nerve fibres in man. Certainly the occurrence of an initial positive wave at the electrode nearer to the point of stimulation does not conflict with the idea that the changes were due to a volley of impulses ascending the nerve towards the recording electrodes. When the region of relative negativity associated with a volley of nerve impulses passes along a nerve which is in a large volume of conducting medium, a similar triphasic variation of potential difference appears between an electrode near to the nerve and one remote from it. The electrode nearer to the nerve becomes first positive with respect to the other, then negative, and finally positive again. A full analysis of this sequence of events has been made (Lorente de No, 1947), which applies to the present recording arrangements even though in these the two electrodes were both relatively close to the nerve and at the boundary of the conducting medium.

Since the findings described above indicated that the changes at the recording electrodes were due to nerve action potentials, and were not due to artefact, experiments were made to determine the type of nerve fibres concerned. The strength of stimulation that was used suggested that the fibres being stimulated had a similar excitability to that of the motor fibres. Stimulation of the motor fibres will produce an ascending as well as a descending volley of impulses, so part or all of the action potentials recorded at the elbow might have been due to these antidromic impulses in motor fibres. The experiment illustrated in Fig. 5 was made to test this point. In it the median nerve was stimulated at the wrist, the action potentials in the muscles of the thenar eminence were recorded from surface electrodes, and fifty records were superimposed. Trace 1, at the top of the records, shows the muscle action potentials, and trace 2 shows time intervals of 1, 5, and 20 msec. and the first big spike indicates the time of stimulation. Trace 3 is a record of the action potentials in the nerve above the elbow, and trace 4 shows the time scale for this record with intervals of 0·1 and 1 msec. The time relation of traces 3 and 4 to that of traces 1 and 2 is shown by the pedestal in trace 2. In Fig. 5A the stimulus used was maximal for the motor fibres to the thenar muscles. In the records in (B), (C), (D), (E), and (F), the strength of stimulus was progressively reduced. In record (D), where the stimulus was only just above threshold for the motor fibres, and when no muscular twitching could be seen elsewhere, the nerve action potential volley has only declined to 70 per cent. of its original size. This suggests that the greater part of the volley recorded in (A) was not in motor fibres but in other fibres which had a lower threshold than that of the motor fibres. In this experiment the subject reported that, with the strengths of stimulus used for records (D) and (E), considerable sensation was produced in the distribution of the median nerve in the fingers. This indicates that where the muscle action potential which was produced by the stimulus used in (A) had disappeared and no evidence of it could be obtained, even with an increased amplification, such as was used in record (F), sensory afferent fibres other than those from muscle were being stimulated. In (F), where the nerve action potential also had virtually disappeared, some sensation was still reported by the subject after each stimulus. Therefore, of the fibres in the median nerve which were stimulated and which had a lower threshold than the motor fibres, some at least were sensory afferent fibres from the fingers. The proportion of afferent fibres from muscles to those from elsewhere was not determined. In interpreting observations such as these it is necessary to consider the division of the nerve into funiculi, which has been investigated by Sunderland (1945), and which makes it possible with weak stimuli to excite alone either motor responses from the thenar muscles or sensations from the fingers, by varying slightly the site of stimulation. In the experiments described the stimulating point was chosen to give the greatest possible motor responses with weak stimuli, and therefore the interpretation of the results is probably not invalidated by any effects of division of the nerve into funiculi.

Discussion

From the number of observations made, it is not possible to draw any useful conclusions about the relation of the amount of subcutaneous fat in the subjects examined to the size of the action potentials which could be recorded. However, the range of build in these subjects was such that it seems reasonable to expect that action potentials of 20 μV. amplitude or more may be recordable under the conditions described in any healthy person. The subject in whom all the action potentials were under 10 μV. and in whose median nerves they were barely detectable had complained some years ago of a patchy anæsthesia and numbness of the left hand which persisted for several months. At that time he was the subject of experiments in which

frequent readings of blood pressure were made and where in some instances cuffs inflated above systolic blood pressure were applied to either arm for considerable periods. At the time of the present examination there were no obvious residual defects in power or sensation, and it seems that if the nerves were damaged in the earlier experiments the recording of nerve action potentials may be a delicate means of detecting minor degrees of damage. The action potentials recorded from the cut and sutured ulnar nerve and from the median nerve known to have been paralysed by the tourniquet are to be described elsewhere but they also suggest that the method may have value in demonstrating small degrees of damage to nerve.

One point of interest has been the apparent homogeneity of the group of fibres being examined by the methods described. The action potential was conducted over a distance of 25 to 30 cm., and might have been expected to show more temporal dispersion than appears in the records. The fact that so little temporal dispersion appears is probably due to the triphasic shape of the recorded wave, since this may have masked later deflections. This is suggested by the fact that, in the few records taken, at the expense of considerable discomfort to the subject, with shocks increased slowly up to 50 and 100 per cent. stronger than those used in the other experiments, the first change in the records which appeared was a reduction in the size of the third phase of the wave and later the appearance of quite clear additional deflections at that time.

Attempts to measure the conduction velocity in the ulnar and median nerves with the methods described have proved on the whole unsatisfactory, on account of the difficulty of making pairs of records which have the same shape from electrodes at different positions on the nerve. Using pairs of records which were nearly superimposable, and timing from the start of the stimulus escape to the first reversal of potential difference between each pair of electrodes, gave differences in latency from which the calculated conduction velocities were in no case outside the range described by Helmholtz and Baxt (1870) for motor nerve fibres in the arm in man. These writers also showed that temperature was a more important factor in producing variation in their results than errors in measurement of either time or distance. It seems, therefore, that no more accurate results are likely to be obtained than those they give without accurate control of temperature, which was not made in these experiments.

Summary

1. In fifteen healthy subjects action potentials have been recorded from electrodes on the skin over the course of the median or ulnar nerve after electrical stimulation of the nerve at the wrist.

2. Sources of artefact are considered, and the methods used for stimulating the nerves and recording the action potentials are described.

3. The type of the fibres from which action potentials may be recorded is considered.

4. It is suggested that the method may have use in the study of minor degrees of nerve injury.

The authors would like to express their gratitude to Dr. E. A. Carmichael, in whose department this work was done. The work was carried out whilst one of us (J.W.S.) was holding a Nuffield Foundation Dominion Medical Travelling Fellowship.

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"INSERTION ACTIVITY" IN ELECTROMYOGRAPHY

WITH NOTES ON DENERVATED MUSCLE RESPONSE TO CONSTANT CURRENT

BY

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Introduction

In clinical electromyography the muscle is examined not only in regard to voluntary activity and "spontaneous" activity, but also as regards the response on mechanical stimulation by the exploring needle electrode. According to Weddell and others (1944), the response of the normal muscle consists of a short outburst of action potentials which can be distinguished from normal motor unit action potentials of neural origin only by the mechanical manner of production. They term these action potentials " insertion motor unit action potentials."

In denervated muscle Weddell and co-workers demonstrated that the outburst lasted appreciably longer, and that the action potentials evoked were identical with those of the spontaneously contracting individual muscle fibres of the denervated muscle, that is, the fibrillary action potentials.

In view of the diagnostic importance of the mechanical irritability, we systematically examined it in the normal, and in the denervated muscle, as well as in different forms of muscular dystrophy. Our report includes also an observation on the response of denervated muscle to constant current.

Material and Method

Material.—The observations in this article are based on examinations of a large number of normal cases; one hundred cases of lower motor neurone lesions of different degree, duration, and ætiology; and fifteen cases of muscular dystrophy (five cases of the common proximal form, eight cases of a distal form, described by Welander (1946), and two cases of *dystrophia myotonica*).

Method.—Coaxial needle electrodes have chiefly been used, vertically suspended to avoid unnecessary bending and pressure. Occasionally, lacquered sewing needles have been used monopolarly, with a reference electrode on an inactive spot a short distance from the muscle being examined. The action potentials were led off to a one-channel balanced condenser-coupled amplifier (time constant about 1/30 sec.) connected to one beam of a cathode-ray tube, the other beam of the tube being connected to an oscillator which recorded the time. The recording methods have been described in detail elsewhere (Kugelberg, 1947; Petersén and Kugelberg, 1949).

The mechanical response of the muscle was tested by gently bending or pressing on the needle electrode. Bipolar stimulation with constant current was used in some experiments. It was not considered necessary to record the form of the current.

Results

Normal Muscle.—On insertion and bending of the needle electrode, the normal muscle responds with a burst of repetitive action potentials (Fig. 1A). Led off with a concentric needle, the amplitude for the latter is, on an average, lower, and the duration shorter, than for ordinary motor unit action potentials, but longer than that of the fibrillary action potential. The mean of the duration of twenty counted potentials, in two different cases was, in the biceps muscle, 4 msec., (the mean for twenty voluntary induced potentials in this muscle ranged between 6·3 and 8·9 msec.; Petersén and Kugelberg, 1949). Many potentials, however, have an amplitude and duration which are identical with either motor unit or fibrillary action potentials.

The frequency of discharge is high at the start, up to 200 per sec. (Fig. 1B). The muscle may then suddenly stop firing without changes in frequency, or with a few irregular or regular beats of lower frequency. The response does not generally outlast the actual shifting of the needle for more than a few tenths of a second. If a light, constant pressure on the needle is applied, the repetitive response may occasionally continue a few minutes longer.

Sixteen subjects without known neuromuscular disorders, between the ages of 20 and 40 years, were systematically examined for mechanical response to the exploring electrode. The extensor group of the forearm, the interosseous muscles, and the biceps were examined altogether at ten different points on each individual. In six of these cases (38 per cent.) it was shown that at one or two points it was possible to elicit activity which, after the needle had been

placed in position, lasted from one to ten minutes or longer. Such discharge was mostly irregular, with a frequency of 1-20 per sec. (Fig. 1C and D). The potentials might be ordinary motor unit potentials as in fasciculation (Fig. 1C). They might also have little amplitude and duration, as in fibrillation (Fig. 1D and E). The activity was distinguished from reflex or voluntary discharge in that it was generally irregular even if the frequency was relatively high, 10-20 per second. With the needle in a fixed position, the action potentials have a constant polarity, indicating that they pass the electrode from the same direction. The activity in question cannot be voluntarily controlled. It does not disappear on relaxation, nor does it increase in frequency on slight voluntary contraction. On the other hand, it appears to be influenced by the needle. A slight pressure or bending may increase the frequency while a discharge is going on, start new ones, or reactivate potentials which had stopped.

Denervated Muscles. *Response on Mechanical Stimulation.*—After the muscle is deprived of its motor nerve supply, insertion potentials of the fibrillary type appear somewhat earlier than spontaneous fibrillation. When the muscle is reinnervated or undergoes morphological changes resulting in fibrosis, the spontaneous fibrillations disappear and, later on, even the fibrillary insertion response.

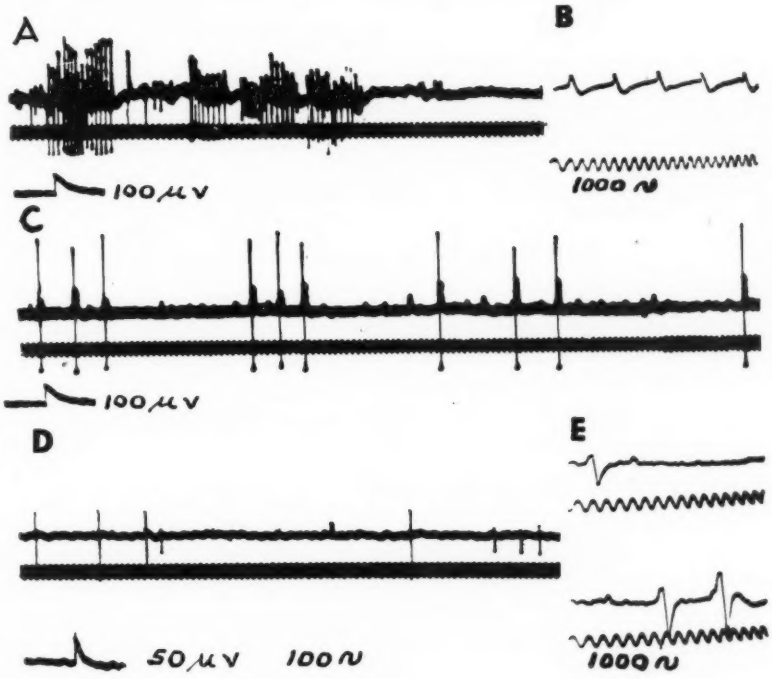

FIG. 1.—Normal muscle. Response on mechanical stimulation. A : Short bursts of repetitive action potentials. B : Detail picture of a burst, with action potentials of 4 msec. duration and frequency of about 200 per sec. C and D: Protracted irregular activity with action potentials similar to ordinary motor unit potentials (C), and fibrillations (D). E : Detail picture of the potentials in D. Amplitude about 100 μ V. Duration 2 and 4 msec.

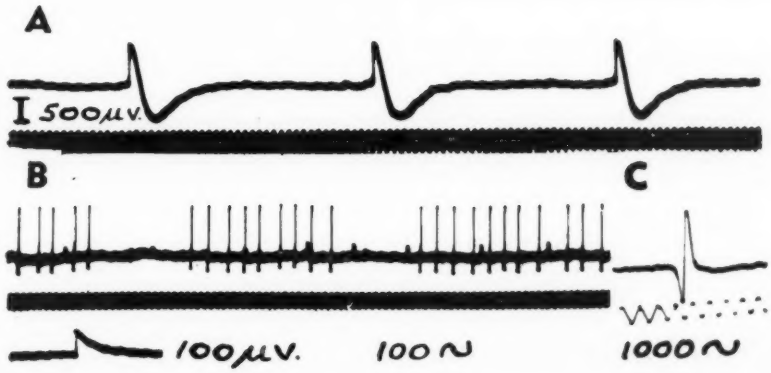

FIG. 2.—Completely denervated muscle. Mechanical response. A : Synchronized activity. Amplitude of potential 1·5 mV. Duration 130 msec. B : The same muscle : repetitive fibrillary activity. C: Detail picture of potential in B.

By the insertion of the needle into an extensor muscle of the forearm in a case with divided radial nerve, a repetitive response of a single fibrillary action potential is evoked (Fig. 2B). The duration is about 1·5 msec., and the amplitude 300 μV. (Fig. 2C). The potential has a duration and amplitude within the limit for the spontaneous fibrillation potentials, and probably corresponds to the activity in a single muscle fibre.

In the same muscle one obtained, however, as a response, potentials of an entirely different appearance (Fig. 2A). A " sharp-rising " phase is followed by long " after-potentials," which are too long to be registered correctly with the type of amplifier used. The amplitude in this case was 1·5 mV and the duration 130 msec. Such potentials occur less often than the insertion fibrillation. They nevertheless constitute a characteristic and common response to

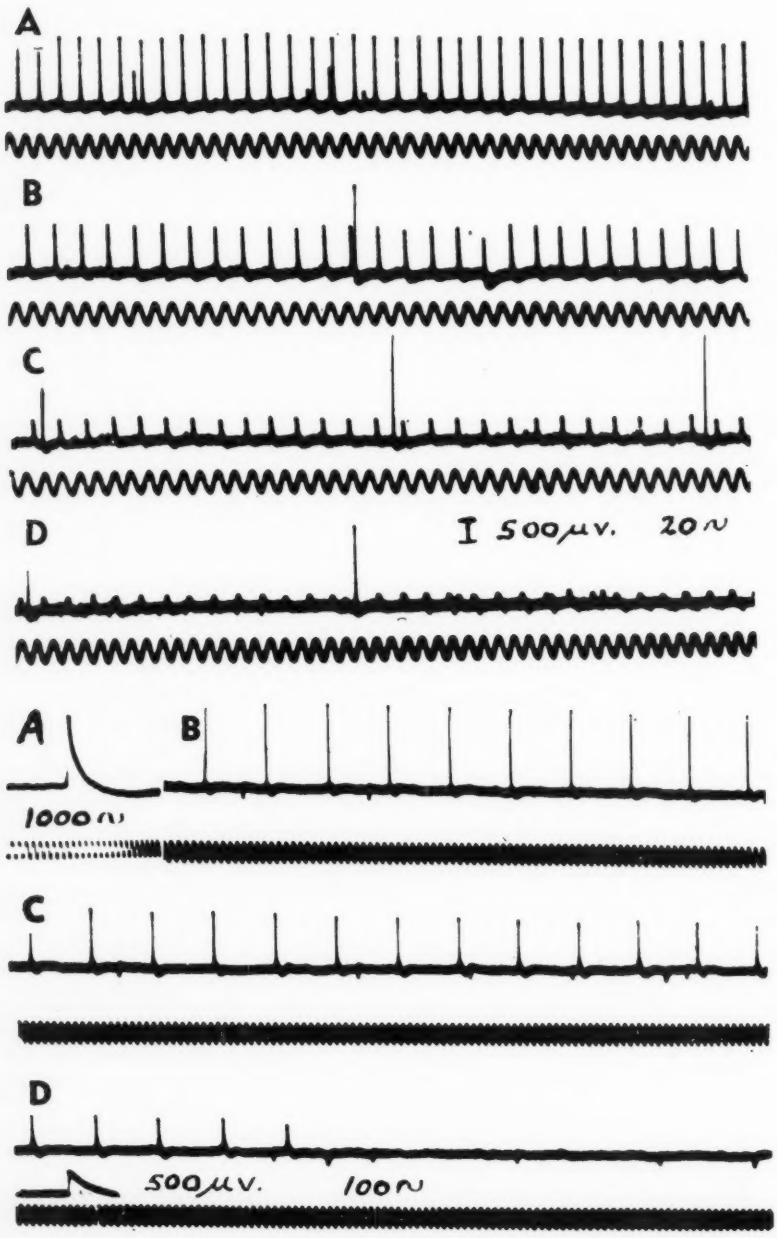

FIG. 3.—Denervated muscle. Repetitive synchronized activity with constant frequency gradually diminishing in amplitude as discharge continues. A : After five minutes. B : After ten minutes. C : After fifteen minutes. D : After twenty minutes.

FIG. 4.—Denervated muscle. Synchronized muscle. A : Detail picture of potential in B. Amplitude 1·8 mV. Duration about 16 msec. B, C, and D : Repetitive discharge with constant rhythm, suddenly ceasing

the stimulation of the denervated muscle.

The maximal values observed for amplitude and duration are 4·5 mV and 200 msec. Otherwise we find all transitions down to the size of the fibrillary action potentials. Led off monopolarly, the first phase of the potentials is most often positive, followed by a negative phase.

The frequency of the impulses in a single series is occasionally as low as 1 per sec., or as high as 100 per sec. It usually ranges between 5 and 20. The rhythm is usually regular, but irregular or random discharges may occur. The duration of an impulse series which follows excitation varies within wide limits. Sometimes a single potential can be followed for 30 minutes or more (Fig. 3). Sometimes the potential is repeated merely a few times. An impulse series may suddenly cease, as a rule without slowing down the rhythm (Fig. 4). Several adjacent foci may discharge with independent rhythm (Fig. 5).

The size that the potential reaches, which may be larger than that of the ordinary motor unit discharge, indicates that it is composed of synchronized activity from many muscle fibres. Often the amplitude of a single repetitive action potential decreases continually, indicating that fibres gradually drop out from the beat (Figs. 3 and 4). Gradual decreasing presupposes that the potential has a certain size. If there are merely a few muscle fibres in the focus, the falling out of a single muscle fibre is naturally more noticeable, whence the potential can be seen to decrease abruptly (Fig. 6). This figure shows in a continuous film a repeating action potential which again and again suddenly decreases in amplitude about 50μV, corresponding to the amplitude of a fibrillary action potential. At the same time the frequency diminishes, but reverts to the original rate when the lost component returns. The change in frequency may be explained by spontaneous fluctuation in the excitability of the focus. When the excitability increases, the frequency is raised, and one or more muscle fibres are recruited, falling out again when the excitability diminishes.

Response to Constant Current.—The slow and prolonged contraction of the denervated muscle in response to stimulation with a constant current was suggested by Bremer (1932) to be a contracture accompanied by a non-oscillatory negativity. Doupe (1942) showed, however, that a repetitive response was readily caused by a constant current. He concluded that the galvanotonus had the character of a tetanus rather than of a genuine contracture. He made no attempt to observe the single action potentials, to establish their type or directly follow their repetitivity.

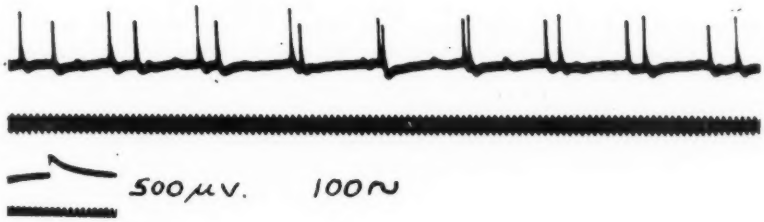

FIG. 5.—Denervated muscle. Two different potentials, discharging independently.

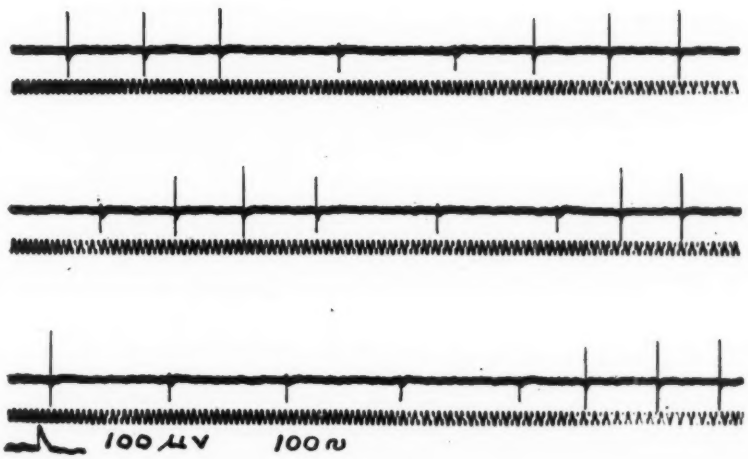

FIG. 6.—Denervated muscle. Repetitive insertion potentials with sudden dropping out of potential components and slowing down of rhythm.

Fig. 7 shows the response to stimulation of the anterior tibial muscle in a case with sciatic nerve lesion leading to complete denervation of the muscle. The strength of the constant current was 10 ma. The activity was led off with a concentric needle electrode 5 mm. distal from the anode, with the cathode proximal to the anode. The current gave rise to a galvanotonus which was accompanied by the same type of activity already described as response to mechanical stimulation, that is, a mixture of fibrillary action potentials and synchronized activity (Fig. 7A). If the current was continued,

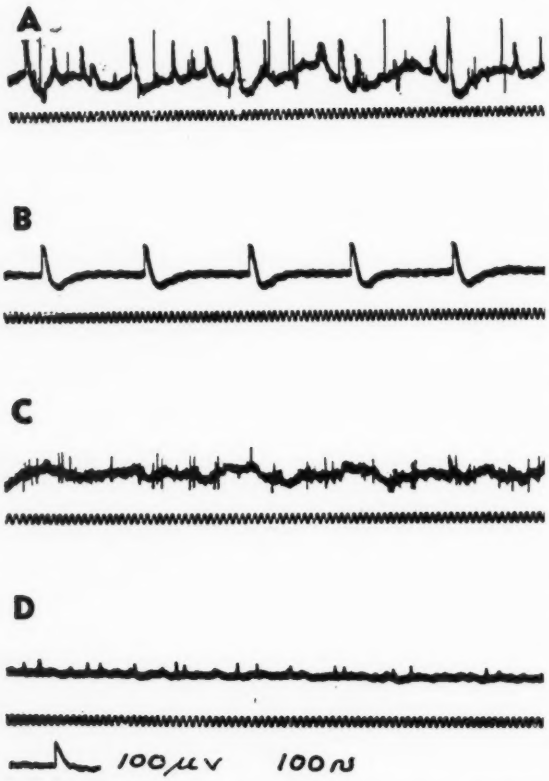

FIG. 7.—Response of denervated muscle to constant current. A : Immediately after closure of current a repetitive discharge of fibrillary and synchronized activity. B : The current still on : After two minutes, only one large potential remains, repeating with almost the same frequency as in A. C and D : The same as A and B, from another muscle, but predominantly of fibrillary type.

the visible muscle contraction gradually subsided, according as one potential after the other dropped out. Finally, merely one relatively large spike (Fig. 7B) remains and goes on repeating with constant frequency, suddenly stopping several minutes later. Sometimes the response is predominantly of the fibrillary type (Figs. 7C and D).

The frequency of the single action potential changes remarkably little, as the contraction of the muscle diminishes owing to its adaptation to the stimulating current. In this way it differs from the reaction of the human motor nerve fibre, which shows a much less rigid response. Under similar conditions in nerve stimulation the frequency changes within wide limits (Kugelberg and Skoglund, 1946).

Muscular Dystrophies.—Irrespective of the type of dystrophy, the mechanical irritability of the muscle tends to diminish according as the wasting increases. The great majority of the potentials that can then be elicited have a small amplitude and duration, thus resembling fibrillary action potentials. The short duration of the insertion potentials may be due to the fact that the number of muscle fibres in the motor units is so reduced by the pathological process that merely a few may be left in each unit. In myopathies the voluntarily induced potentials undergo a similar change (Kugelberg, 1947, 1949).

In muscles where the wasting process has not gone so far, the mechanical irritability differs somewhat in the various forms of dystrophy. In the common proximal form the response resembles that of the normal muscle, except that the fibrillary type of response predominates. A short outburst of high-frequency discharge, or occasionally, prolonged repetitivity is obtained. In the distal form the irritability may here and there be intensified. It may then be considerably easier to elicit prolonged high-frequency or low-frequency responses. Occasionally, as is usual in myotonia, the recorded activity may apparently continue indefinitely after the insertion of the needle. In such cases it is difficult to determine whether the activity has really been initiated by the mechanical irritation or whether it is spontaneous.

In dystrophia myotonica the mechanical irritability, as is well known, is greatly intensified (Brown and Harvey, 1939 ; Denny-Brown and Nevin, 1941 ; Buchthal and Clemmesen, 1941). A prolonged response can be obtained anywhere in the myotonic muscle. A high-frequency response predominates, but prolonged slow, regular or irregular, discharges occur. The action potentials may be of the fibrillary type or, more or less, of the motor unit type. Large repetitive potentials, probably due to synchronized activity from several motor units, may occasionally be seen.

There are thus similarities between the distal form of muscular dystrophy and the denervated muscle as well as myotonia, as regards the mechanical irritability. However, no involvement of the lower motor neurone has been found at autopsy (Welander, 1949), nor any clinical myotonic signs which could explain these similarities. We may therefore assume that

during some stage of the dystrophic process the irritability of the muscle may be increased in this disease.

Discussion

The prolonged repetitive activity observed when exploring apparently normal muscles with needle electrodes is probably induced by mechanical stimulation and injury of muscle fibres and intramuscular nerve branches. The phenomenon is of practical importance, as it may be a source of error. The repetitivity, if prolonged for many minutes, may be indistinguishable from either spontaneous fasciculation or fibrillation, depending on the appearance of the potentials. In normal muscles, however, there are but few points from which prolonged repetitivity can be induced in this manner.

The large synchronized activity in denervated muscles which occurs as a response to mechanical and electrical stimulation has not been observed in the normal muscle. A greatly increased irritability is doubtless necessary to bring about this result.

This form of activity almost invariably co-exists with insertion fibrillation, and the frequency of discharge in both is similar. It may be presumed that the synchronized activity is actually a synchronized fibrillation. Its occurrence in completely denervated muscle shows that synchronization, at any rate here, takes place extraneurally, being possibly induced electrically from some fibres acting as "pacemakers." The spontaneously occurring synchronized activity described by Adrian and Gelfan (1933) in frog muscle in the case of calcium deficiency, is closely related. So also is the spontaneous synchronized discharge observed by Harvey and Kuffler (1944) in the denervated muscles of the hypothenar eminence in one patient. In that case the action potentials could be led off with surface electrodes, and the accompanying muscle twitches could be observed through the skin with the naked eye. They assumed that the spontaneous activity may have originated in the region of the motor end plates. However, since the synchronized discharge caused by insertion is a typical and common symptom of the denervated muscle, the spontaneous synchronized activity seems to be rare. Its appearance is of definite diagnostic value.

The electromyographic diagnosis should not be based merely on single factors, such as the type of insertion activity and the occurrence of spontaneous activity, which, though often valuable indications, may not be specific signs. The duration, amplitude and form of voluntarily induced potentials must also be considered, as well as the number of recruited spikes in the picking-up range of the electrode on maximal voluntary contraction, evaluated against the force exerted. When all these factors are judged in relation to the symptoms and signs observed in the clinical examination, electromyography will give exact and conclusive diagnostic information.

Summary

The response of normal, denervated, and dystrophic muscle to mechanical stimulation by the exploring concentric needle electrode has been investigated, as well as the response of the denervated muscle to stimulation by a constant current.

Normal Muscle.—The response consists of a high-frequency discharge of action potentials. The average amplitude and duration is somewhat less than that of motor unit action potentials, though potentials of the same size as motor unit or fibrillary action potentials are common. The response does not generally outlast the actual shifting of the needle by more than a few tenths of a second. An irregular response lasting several minutes, which may be indistinguishable from either fasciculation or fibrillation, occasionally occurs.

Denervated Muscle.—(a) Needle. The response consists of an often prolonged repetitive discharge of the fibrillary type and synchronized activity discharging chiefly at a constant rhythm with a frequency of 1-100 per sec. The synchronized discharge may continue for 20 minutes or more, during which time amplitude and duration generally diminish. The synchronization is brought about extraneurally. (b) Constant Current. The response consists of fibrillary and synchronized repetitive activity which accompanies the galvanotonus.

Dystrophic Muscle.—The mechanical irritability tends to diminish according as the wasting increases. Otherwise, the irritability is rather normal in the common proximal form, while in the distal form it may be increased here and there, and in the myotonic muscle is greatly increased. The action potentials evoked are often of the fibrillary type in all three forms.

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AN EXPERIMENTAL INVESTIGATION OF THE CONNEXIONS OF THE OLFACTORY TRACTS IN THE MONKEY

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The great expansion of the cerebral cortex which has taken place in higher primates has brought about a considerable displacement of structures on the base of the telencephalon, and the precise comparison of certain areas in this part of the brain with those in lower mammals has been a matter of some difficulty. This is particularly true of the olfactory areas which lie on the orbital aspect of the frontal lobe and the adjacent part of the temporal lobe. Although this part of the brain in primates has been subjected to detailed cyto-architectural and myelo-architectural examinations (Rose, 1927b, 1928 ; Beck, 1934, and others), the areas directly related to olfaction have never been clearly defined.

It has been generally believed that the olfactory peduncle divides into two main fibre bundles : the lateral olfactory stria, through which fibres pass to the uncus and possibly the hippocampal formation, and the medial olfactory stria, through which fibres reach the subcallosal gyrus, anterior perforated substance, and septum. This specification of the olfactory areas, derived from observations made chiefly in lower mammals with normal material, has not until recently been subjected to experimental verification. As regards the olfactory connexions in lower mammals, Cajal (1901 and 1911) attributed no importance to the medial olfactory stria and denied the existence of any direct olfactory fibres to either the septum or the hippocampus. Recent experimental evidence supports Cajal's point of view. Rose and Woolsey (1943) and Fox and others (1944) stimulated the olfactory bulb in carnivores and recorded potential changes in the prepiriform cortex, the peri-amygdaloid region, and the olfactory tubercle, but none from the septum and hippocampus. Le Gros Clark and Meyer (1947), by using a silver technique for tracing the terminal degeneration in olfactory fibres after ablation of the olfactory bulb in the rabbit, obtained similar results. In addition they observed, in the bed nucleus of the stria terminalis and central amygdaloid nucleus, bilateral degeneration of olfactory terminals apparently passing through the anterior limb of the anterior commissure. The present study has been undertaken to map out the connexions of the olfactory bulb in the monkey's brain as precisely as possible with the same silver technique.

Material and Methods

Three macaque monkeys (*Macaca mulatta*) and two immature Guinea baboons (*Papio papio*) were used. The operative technique was similar in all cases : under nembutal anæsthesia and with the usual aseptic precautions a large right frontal bone flap was reflected ; the frontal lobe of the hemisphere was carefully retracted, and the olfactory peduncle, lying on the ventral surface, was severed. In some cases there were small incidental lesions due to contusion on the convexity of the cerebral cortex, but it was possible during the subsequent analysis to distinguish between the degeneration which resulted from these lesions and that in the olfactory areas. The macaques were allowed to survive four, five, and seven days before decapitation, the baboons three and five days. Brains were removed immediately after death and fixed in 10 per cent. formol-saline for three weeks. They were then divided into blocks of convenient size and a large number of frozen transverse sections were cut, which together formed a complete series through the base of the telencephalon. Most of the sections were impregnated by the ammoniacal silver method of Glees in order to show degeneration of axons and their terminals ; other sections taken from the same levels were prepared by the myelin technique of Weil, and also by a Nissl stain, to facilitate identification of the several nuclear masses and fibre systems. In addition, complete series of transverse sections through the normal telencephalon of *Macaca*, stained by the Weigert and cresyl violet methods, were available for study.

In all cases, sections of both sides of the brain were taken and treated identically. Thus, sections of the left or unoperated side of the brain were available for use as controls, and were carefully compared with the corresponding sections of the right side of the brain. In this way, errors which might result from erratic impregnation simulating degeneration were avoided as far as possible. Further, the extent and distribution of degeneration in different cases with different survival

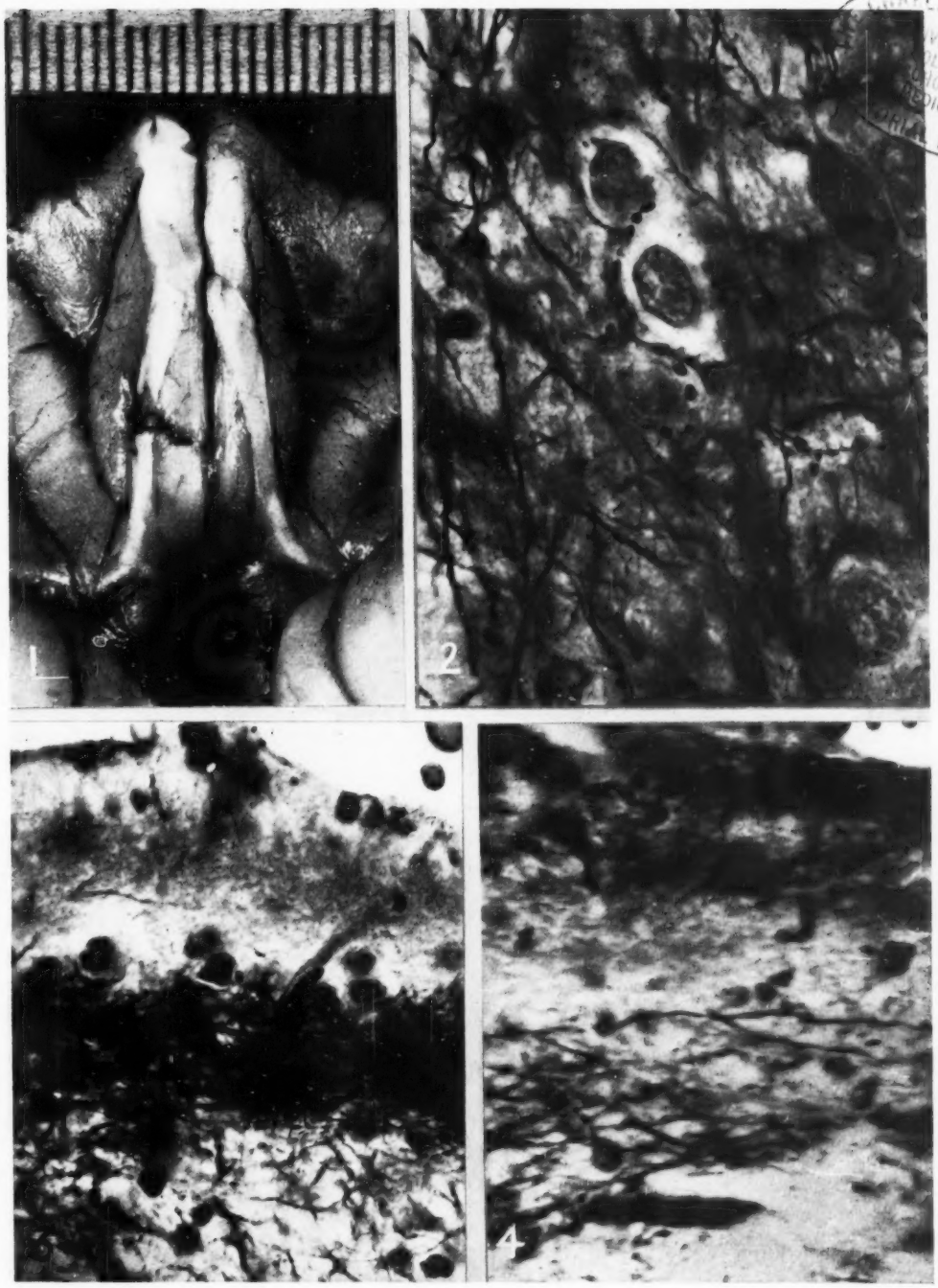

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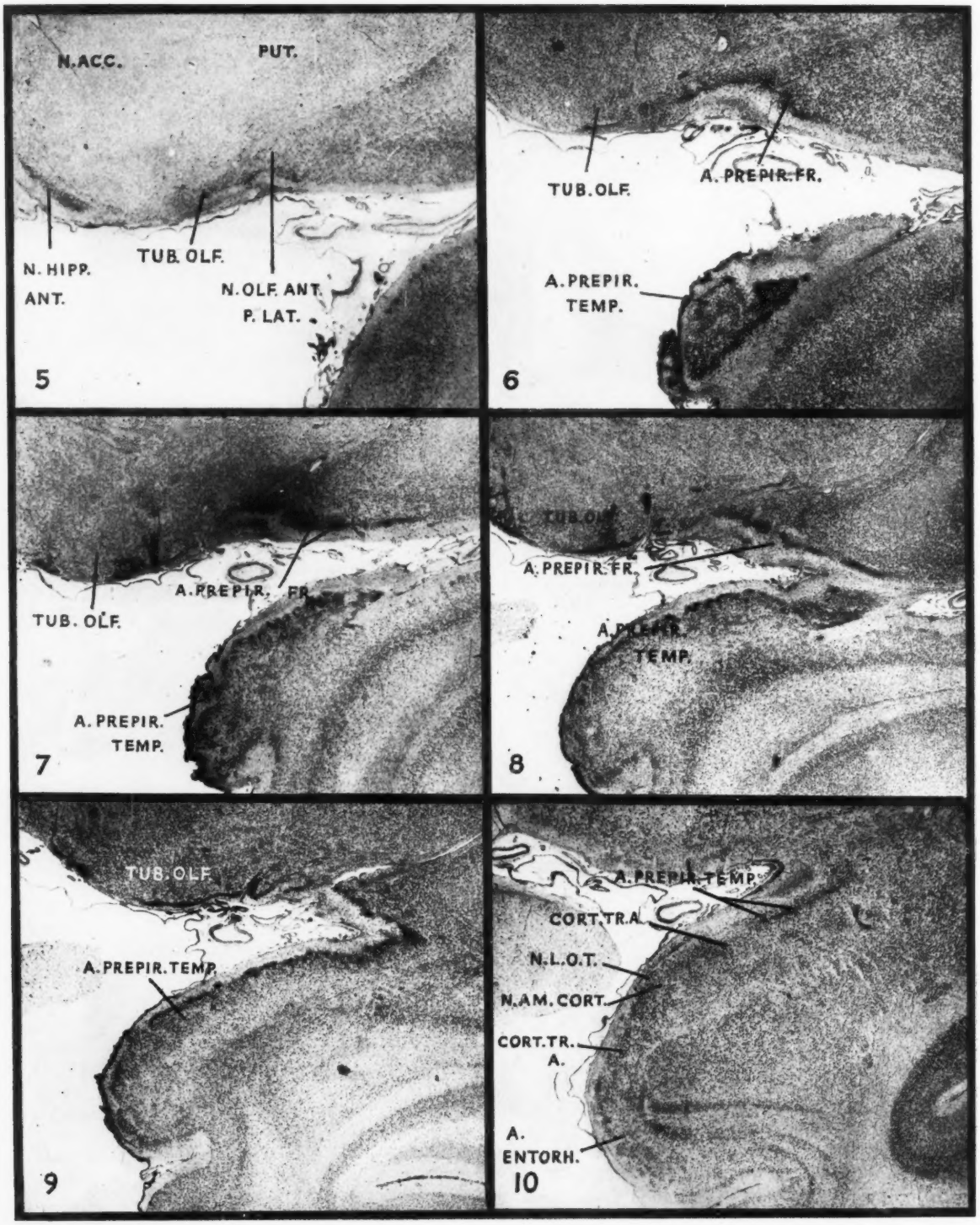
FIG. 1.—Base of frontal lobe of *Macaca* after operation, showing the right olfactory peduncle transected with very little damage to the gyrus rectus, × 2½.

FIG. 2.—Terminal degeneration around cells of the bed nucleus of the stria terminalis of *Papio*, five days after transection of the olfactory peduncle. Note that fibres of the stria are intact, × 1,100.

FIG. 3.—Normal olfactory fibres in the superficial layer of temporal prepiriform cortex of *Papio*, × 700. Compare Fig. 4, which is the operated side of the same case.

FIG. 4.—Temporal prepiriform cortex of *Papio* five days after section of the olfactory peduncle, × 700. There is already almost complete degeneration of olfactory fibres, and only brown débris and a few tangential fibres remain.



FIGS. 5–10.—Representative transverse sections through the olfactory areas of the basal telencephalon of *Macaca*. Nissl stain. All × 10 except Fig. 6 which is × 13. In Fig. 10 the posterior extremity of the temporal prepiriform area (which goes over into medial amygdaloid nucleus) and of the dorsal part of the cortico-amygdaloid transition area are shown.

periods were found to be very consistent. The early stages of degeneration are recognizable chiefly in the terminals and the very fine preterminal fibres; later, these are entirely disintegrated and the coarser fibres break up. By thus having a series of cases showing different stages of degeneration, it is possible to reconstruct fairly accurately the course and termination of the fibre pathways involved.

Observations

The course and distribution of degenerative changes following sectioning of the olfactory peduncle will be described by reference to a series of transverse sections through the telencephalon of *Macaca*, the levels of which are shown in Fig. 17. The results of experiments on *Papio* are so similar to those on *Macaca* that no separate description is necessary.

In general, we have followed the terminology used by Crosby and Humphrey (1941) for the corresponding parts of the human brain, and that used by Lauer (1945) for the macaque brain, although our interpretation of the homologies of certain regions differs in some respects from theirs. Most of the primary olfactory areas are illustrated in the Nissl sections shown in Figs. 5 to 10. As far as the cortex of the piriform lobe is concerned, we have not been able to apply directly the cyto-architectonic subdivisions described in different species of mammals by Rose (1927a and b, 1928). Following the recommendation of Brodmann (1909) and others, we have recognized only two cortical areas in the anterior part of the hippocampal gyrus, the prepiriform area and the entorhinal area (Fig. 17). Also, in accordance with the current terminology, we have included the so-called peri-amygdaloid area, which has been regarded by some authorities as part of the piriform lobe cortex, in the amygdaloid complex.

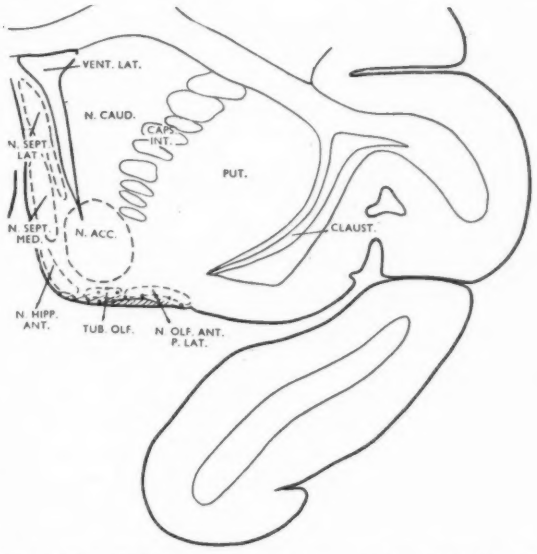


FIG. 11.—Outline of transverse section through the cerebral hemisphere of *Macaca* at the level of the septum and the anterior margin of the olfactory tubercle. In this and the other text figures, degeneration of terminals is indicated by dots, and that of fibres by hatching.

Level 1 (Figs. 5 and 11).—At this transverse level the olfactory tract has already deviated somewhat laterally from the position it occupies further forward where the olfactory peduncle joins the orbital surface of the hemisphere. It is made up of a flattened dense mass of fibres which are obliquely cut, so that it is not possible to recognize the different component parts of the tract described by Lauer (1945) and others. The tract overlies the deeply-stained cells of the anterior olfactory nucleus, the lateral part of which grades laterally into neocortex. Only a very slight depression on the surface of the brain, which corresponds to the anterior extremity of the rhinal fissure in lower

ABBREVIATIONS USED IN ALL FIGURES

a. entorh.	entorhinal area.
a.preop.med.	medial preoptic area.
a.prepir.fr.	frontal prepiriform area.
a.prepir.temp.	temporal prepiriform area.
caps.int.	internal capsule.
ch.opt.	optic chiasma.
claust.	claustrum.
com. ant.	anterior commissure.
com.ant.l.ant.	anterior limb of anterior commissure.
cort. tr.a.	cortico-amygdaloid transition area.
forn.	fornix.
lim. ins.	limen insulæ.
n. acc.	nucleus accumbens.
n.am.b.a.	accessory basal amygdaloid nucleus.
n.am.b.l.	lateral part of basal amygdaloid nucleus.
n.am.b.m.	medial part of basal amygdaloid nucleus.
n.am.cent.	central amygdaloid nucleus.
n.am.cort.	cortical amygdaloid nucleus.
n.am.med.	medial amygdaloid nucleus.
n. caud.	caudate nucleus.
n.diag.b.	nucleus of the diagonal band.
n.hipp.ant.	anterior hippocampal nucleus.
n.l.o.t.	nucleus of the lateral olfactory tract.
n.olf.ant.p.lat.	lateral part of anterior olfactory nucleus.
n.sept.lat.	lateral septal nucleus.
n.sept.med.	medial septal nucleus.
n.str.term.	bed nucleus of the stria terminalis.
pall.	pallidum.
put.	putamen.
sulcus entorh.	entorhinal sulcus.
sulcus rh.	rhinal sulcus.
tr.op.	optic tract.
tub.olf.	olfactory tubercle.
vent. lat.	lateral ventricle.

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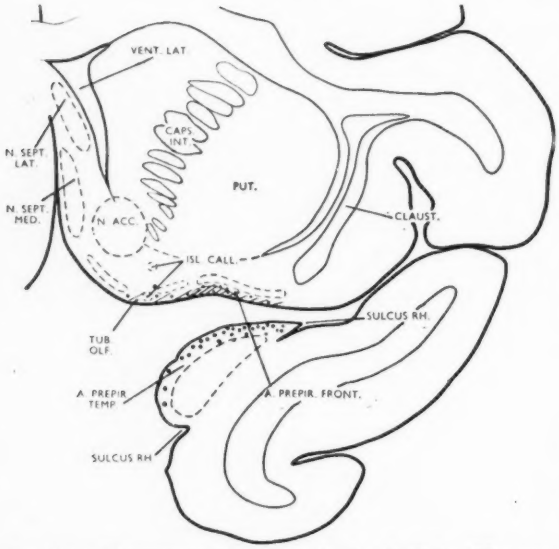

FIG. 12.—Transverse section at the level of the olfactory tubercle and the anterior margin of the prepiriform area.

mammals, marks this transition. On the medial side of the tract the medial part of the anterior olfactory nucleus has been replaced by the rostral extremity of the olfactory tubercle, and the latter is adjoined by the large cells of the anterior hippocampal nucleus which reach upwards towards the septal nuclei. A medial fascicle from the olfactory tract is clearly defined, extending as far as the superficial layer of the anterior hippocampal nucleus. A smaller lateral fascicle lies superficial to the lateral part of the anterior olfactory nucleus; it does not extend as far laterally as the isocortex.

Seven days after transection of the olfactory peduncle, many, but not all, fibres of the lateral olfactory tract are degenerated. There is almost complete disintegration of the axons in the lateral and medial fascicles, and even under low magnification a definite loss of fibres is apparent when the section is compared with that of the normal side. Degenerating fibres of the medial fascicle can be traced into the superficial layer of the anterior hippocampal nucleus, but fibres among the cells of the nucleus are intact. Some degeneration is seen in that part of the anterior olfactory nucleus which lies immediately above the olfactory tract, and which appears to be equivalent to the pars externa of the anterior olfactory nucleus in lower mammals. Otherwise the fibre plexus within the anterior olfactory nucleus is normal.

In the three-day experiment very little change is seen in the fibres of the tract, but degeneration of terminals is more distinct. It is most striking in the olfactory tubercle, where there are numerous disintegrating fine fibres and enlarged terminal boutons in the superficial layer; these extend into the pyramidal cell layer, and some penetrate as deeply as the polymorph layer (particularly in the vicinity of the olfactory tract). Further medially, degenerative changes are again confined to the superficial layer of the anterior hippocampal nucleus; only in one case, complicated by an incidental lesion in the cerebral cortex, was degeneration found among the cells of the nucleus itself. The septal nuclei, including the nucleus accumbens, remain entirely normal.

Level 2 (Figs. 7 and 12).—At this level, the lateral fascicle of the olfactory tract is much more extensive and is accompanied by the deeply-stained band of pyramidal cells of the prepiriform cortex, which has replaced the lateral part of the anterior olfactory nucleus. The olfactory tubercle is enlarged considerably and shows well-defined lamination close to the tract, while more medially the islands of Calleja are very conspicuous, sometimes lying close to the surface of the brain. The short medial fascicle of the olfactory tract ends before the medial part of the tubercle is reached. The rostral extremity of the prepiriform area on the temporal lobe is limited on both sides by the curved anterior part of the rhinal fissure. In silver preparations the first layer of the prepiriform area consists of a dense mass of fine fibres which turn inwards towards the pyramidal cell layer, becoming less numerous

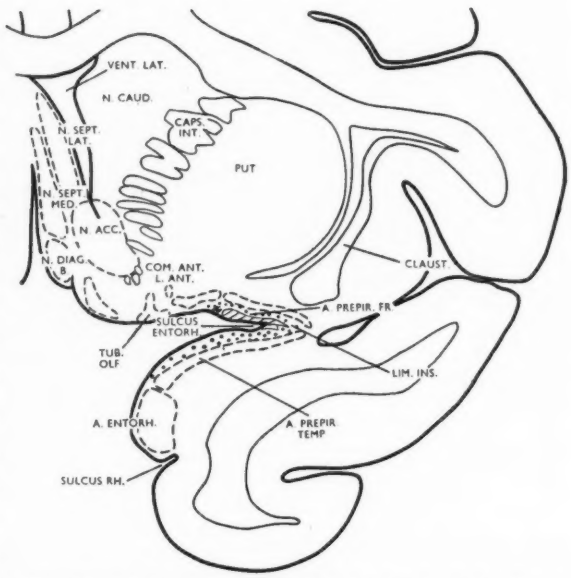

FIG. 13.—Transverse section at the level of the limen insulæ.

on either side as the rhinal fissure is approached. In Nissl sections this area is characterized by its darkly stained, slightly corrugated band of pyramidal cells overlying the isocortex of the temporal lobe (Figs. 6 and 7).

Degeneration at this level is best seen in the four- and five-day experiments. It is particularly marked in the superficial layers of the prepiriform cortex of the temporal lobe, the fine fibres of which show almost complete drop-like disintegration. The extent and distribution of this degeneration corresponds precisely to that of the penetrating fibres just mentioned as occupying the superficial cortical layer of the normal side. Isolated degenerating fibres pass into the pyramidal cell layer. The degeneration in the prepiriform area of the temporal lobe is considerably more severe than in the prepiriform area on the orbital surface of the frontal lobe. In the latter region the lateral fascicle is beginning to break up and terminal degeneration is again confined to the superficial and plexiform layers. The lateral part of the tubercle also shows in its plexiform layer a large number of disintegrating terminals. Some of these penetrate into the deeper layers of the tubercle and into the more superficially situated islands of Calleja. The medial part of the tubercle, the septal nuclei, and the nucleus accumbens are all normal.

Level 3 (Figs. 8 and 13).—At this level the frontal lobe becomes connected with the temporal lobe through the limen insulæ. From the tract a large component passes to the junction of the frontal and temporal lobes in the entorhinal sulcus and is continuous with the dense fibre feltwork in the superficial layer of the adjacent part of the prepiriform area of the temporal lobe (Fig. 3). Thus, even normal preparations make it apparent that the finer fibres in the superficial layer of this part of the prepiriform area are formed by the terminal arborizations of axones of the lateral olfactory tract. Some fibres of the lateral olfactory tract spread across towards the insula, accompanied by the pyramidal cell layers of the prepiriform cortex of the frontal and temporal lobes. The cyto-architectural features of these areas are clearly seen in Nissl preparations (Fig. 8). The lateral olfactory tract also contributes a short medial fascicle to the olfactory tubercle. The anterior limb of the anterior commissure is seen to consist of three small bundles of fibres situated close to the tubercle and ventro-lateral to the nucleus accumbens.

The extent and distribution of degeneration at this transverse level is well seen four and five days after section of the olfactory peduncle. Examination with low power reveals a marked difference in intensity of staining between olfactory fibres in the normal and operated sides. Fibres on the normal side are stained a deep black, while those on the side of lesion are a much lighter brownish colour. Under high magnification an unbroken band of degenerating fibres and terminals is seen in the superficial and plexiform layers of the prepiriform cortex, extending from the lateral third of the orbital surface of the frontal lobe as far as the limits of the entorhinal area on the dorsal surface of the temporal lobe. In the entorhinal area itself only very few, isolated, degenerating fibres are seen at its margin of contact with the prepiriform area. In both these experiments with four and five days' survival after operation many of the thick fibres of the olfactory tract itself are still intact, whilst the fine terminal fibres in the superficial cortical layers of the temporal lobe all show drop-like disintegration. This confirms previous observations that terminal arborizations of axones degenerate some time before the axones themselves are affected. The fascicle of the olfactory tract which spreads towards the insula is degenerated, but it does not actually reach the isocortex of the insula, and there is no evidence of degeneration in any of the cortical layers of the insula itself. Compared with more anterior levels, the tubercle receives few olfactory fibres, and these are localized to the part nearest the olfactory tract. The septal nuclei and nucleus accumbens are again normal. The bundles of the anterior limb of the anterior commissure are cut transversely, and hence it is not possible to detect with certainty any degeneration in them.

Level 4 (Fig. 14).—At this level the lateral olfactory tract can no longer be observed macroscopically on the surface of the brain. In sections the main bulk of the tract is seen to have swung around to terminate in the rostral part of the prepiriform area on the temporal lobe, as described in the preceding levels. The remainder of the lateral olfactory tract, much reduced in size and cut somewhat obliquely, lies in the entorhinal sulcus, and a fascicle (cut longitudinally) passes from the main tract along the superficial layer of the prepiriform area of the temporal lobe. The pyramidal cell layer of the prepiriform cortex is adjoined ventro-medially by the cortical transition area, which overlies the foremost extremity of the basal accessory amygdaloid nucleus.

In the four- and five-day experiments most of the fibres of the lateral olfactory tract in the angle between the frontal and temporal lobes are in process of degeneration, and the superficial layer of the prepiriform cortex on the dorsal surface of the temporal lobe has much the same appearance

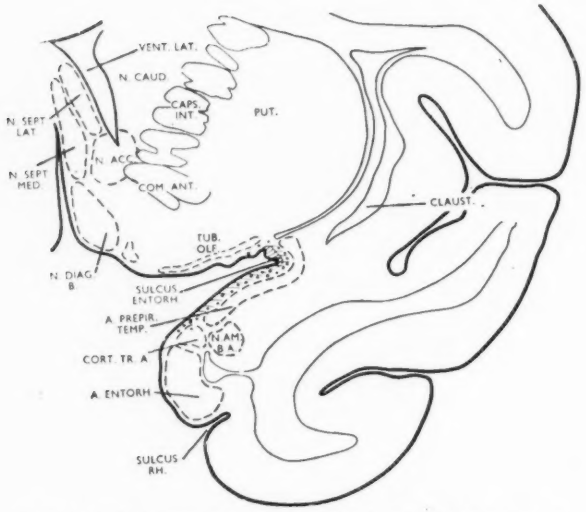

FIG. 14.—Transverse section at the level of the anterior margin of the amygdaloid formation.

as in the preceding level. Degenerating fibres in the superficial layer of the cortex terminate as far ventrally as the transition area. The entorhinal area is quite normal. The distribution of olfactory fibres to the tubercle is insignificant at this level, only the most lateral part of this region, adjacent to the lateral olfactory tract, being affected. More medially, the superficial fibres which surround the tubercle are normal, and appear to be derived from the most ventral fibres of the external capsule.

The seven-day case shows a severe loss of fibres in the superficial and plexiform layer of the prepiriform cortex when compared with the normal side, and in those fibres which are left degeneration is far advanced (Figs. 3 and 4). Some normal fibres remain, which are probably tangential fibres arising (according to Cajal) from nerve cells in the first cortical layer. Again, as in the rabbit, degeneration is confined to the outermost and plexiform layers of the prepiriform cortex, thus indicating an axo-dendritic contact between olfactory terminals and cells of the piriform cortex. There is no evidence of fibre or terminal degeneration elsewhere at this level.

Level 5 (Fig. 15).—This level corresponds to the most caudal part of the crossing of the anterior commissure. The prepiriform cortex has been replaced by the cortico-medial group of amygdaloid nuclei, and the various elements of the latter can here be mapped out clearly. The lateral olfactory tract is much reduced in size, its fibres occupying a similar position to that described in the preceding level. The fascicle passing from the main tract now surrounds the cortico-medial amygdaloid group. The bed nucleus of the stria terminalis has reached its greatest extent, beginning at the dorso-medial aspect of the internal capsule, near the caudate nucleus, and passing around the caudal part of the anterior commissure to merge ventrally with the medial preoptic region.

Four and five days after section of the olfactory peduncle, degenerating fibres of the lateral olfactory tract spread into the medial amygdaloid nucleus, and fine terminal fibres showing drop-like disintegration surround its nerve cells. That part of the nucleus which is close to the tract receives more olfactory fibres than the lateral part, where the fibre plexus is almost intact. In the peri-amygdaloid fascicle of the tract, degeneration is very marked. A number of fibres terminate in both parts of the nucleus of the lateral olfactory tract, only the posterior part of which is shown in Fig. 15. Degenerating fibres and terminals remain in the superficial

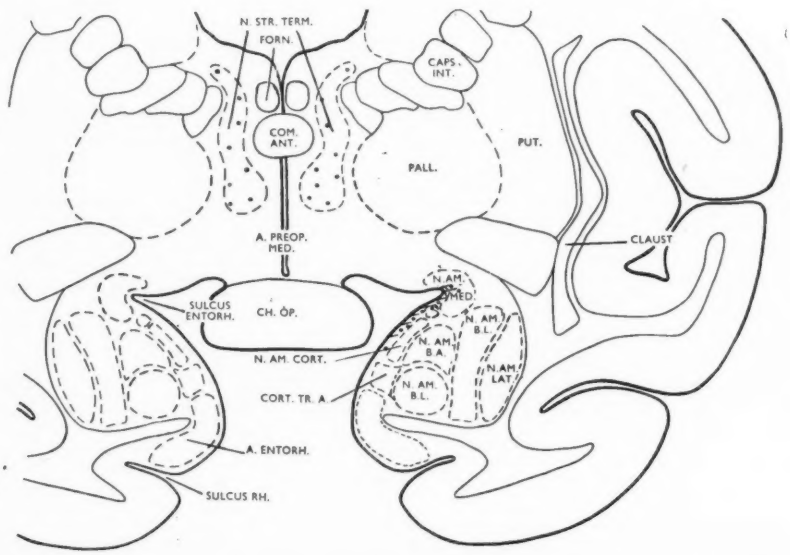

FIG. 15.—Transverse section at the level of the optic chiasma and the middle of the amygdaloid formation.

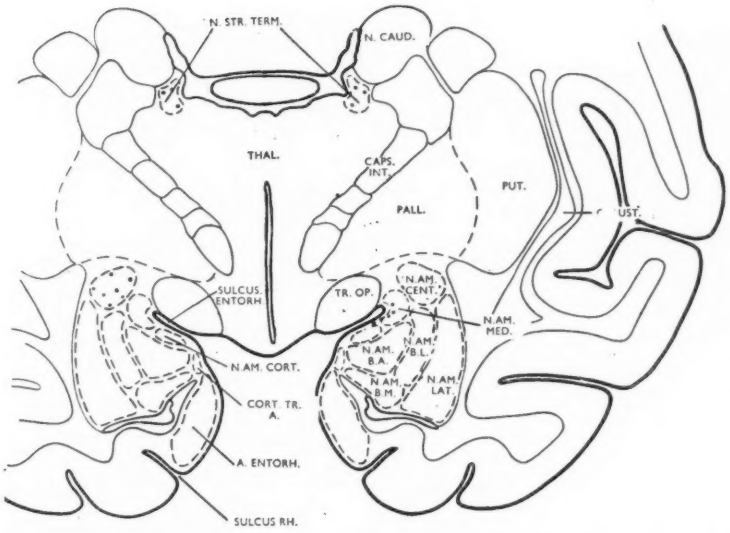

FIG. 16.—Transverse section at the level of the caudal part of the amygdaloid formation.

layer of the cortical amygdaloid nucleus and make no contact with the cell bodies of the nucleus. They can be traced as far as the transition area. The entorhinal area is apparently quite unaffected.

There is bilateral terminal degeneration in the nucleus of the stria terminalis. Much of the fibre plexus within the nucleus has remained intact, but a number of fine, degenerating, terminal fibrils surround the nerve cells of the nucleus in typical drop-like disintegration (Fig. 2). The fibres of the stria terminalis itself are normal. In the seven-day experiment the sections have been cut slightly more caudally. The bed nucleus of the stria terminalis appears as two circumscribed masses of small cells, the larger in the medial preoptic region and the other, which goes over eventually into the central amygdaloid nucleus, between the caudate nucleus and the anterior extremity of the thalamus. Few degenerating fibres are seen just medial to the internal capsule, but the severity of degeneration increases as the nucleus of the stria terminalis in the medial preoptic region is approached. The boundaries of the nucleus are not very distinct, and signs of degeneration appear to extend into the periventricular region and into what is usually considered a part of the medial preoptic nucleus. In this case, too, the preoptic region and nucleus of the stria terminalis are affected bilaterally. The fibre plexuses of the lateral preoptic region, hypothalamus, and other areas are intact.

Level 6 (Fig. 16).—This level corresponds approximately to the posterior third of the amygdaloid complex. The central amygdaloid nucleus has now appeared and the baso-lateral group has expanded at the expense of the cortico-medial group of nuclei. The nucleus of the stria terminalis lies between the caudate nucleus and the thalamus.

Olfactory fibres and terminals become progressively more sparse posteriorly, so that at this level in the four- and five-day experiments degeneration in the medial and cortical amygdaloid nuclei is much less severe than in the preceding level. In the bed nucleus of the stria terminalis and the central nucleus there is bilaterally a breaking-up of some of the fine intrinsic fibres. The other amygdaloid nuclei, the entorhinal area, and the hypothalamus show no signs of degeneration.

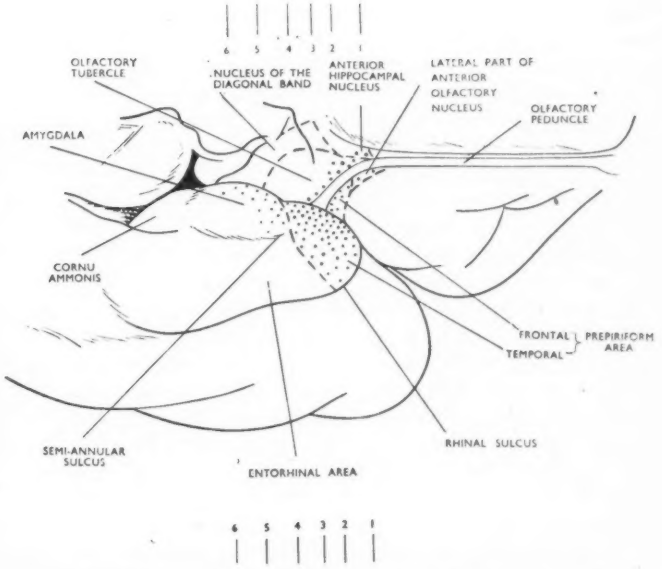

FIG. 17.—The basal telencephalic areas of *Macaca*, with the temporal lobe somewhat retracted to display the distribution of olfactory terminals (dotted).

Discussion

The experimental evidence presented in the preceding pages enables us to give a more accurate account of the central connexions of the olfactory tracts in the monkey's brain than has previously been possible. Before discussing the different areas of termination separately, we propose to recount the course of fibres of the olfactory tracts according to these observations. In most cases the olfactory peduncle was severed just before it fuses with the orbital surface of the frontal lobe (Fig. 1), and thus fibres which the anterior olfactory nucleus may contribute to the olfactory tract had also been interrupted. As the lateral olfactory tract continues caudally, a medial and a lateral fascicle are given off. The medial fascicle extends into the plexiform layer of the anterior hippocampal nucleus, but it does not reach the septal nuclei or the isocortex of the gyrus rectus, as has been suggested by Lauer (1945) from normal preparations. The lateral fascicle terminates in the superficial layer of the frontal extension of the prepiriform cortex, not extending as far as the neocortex of the orbital gyri (as it is also stated to do by Lauer).

As the olfactory tubercle is approached the lateral olfactory tract becomes wider. Its most medial fibres terminate in the rostral and lateral part of the olfactory tubercle, but the great majority deviate laterally towards the limen insulæ, skirting the anterior perforated space. As in the rabbit, we have not been able to distinguish a bifurcation of the tract, with the formation of a separate " medial root " to the septal region in the macaque brain. Different components of the tract can be distinguished within the olfactory peduncle, but at the more caudal levels no clear division into roots is recognizable. Reaching the limen insulæ, the lateral olfactory tract disappears from the surface of the brain. In silver sections, however, it is seen that at this point the terminal arborizations of the great majority of fibres (not visible in myelin preparations) are folded over and extend forward over the dorsal surface of the temporal lobe to end in the prepiriform cortex which forms the anterior part of the hippocampal gyrus (gyrus ambiens in man). Thus at some transverse levels (for example see Fig. 12) the olfactory tract itself is seen on the orbital surface of the frontal lobe and (in the same section) its terminations on the temporal lobe. Some fascicles continue caudally in the entorhinal fissure to the peri-amygdaloid region (or gyrus semilunaris), where they terminate in the superficial nuclei of the cortico-medial group of the amygdaloid complex. The anterior limb of the anterior commissure (or " intermediate olfactory stria ") appears to be the pathway of olfactory fibres to the bed nucleus of the stria terminalis, which extends at one end into the preoptic region and at the other to the central amygdaloid nucleus.

Olfactory Tubercle.—There has been some divergence of opinion whether the olfactory tubercle received fibres from the olfactory tract (Cajal, 1901 ; Elliot Smith, 1909, and others). Recently Le Gros Clark and Meyer (1947) demonstrated that extirpation of the olfactory bulb in rabbits is followed by terminal degeneration in the olfactory tubercle, a finding which supports the experimental physiological evidence of Fox and others (1944) in the cat. In our experiments, sectioning of the olfactory peduncle in the monkey was followed by degeneration in the anterior and lateral parts of the tubercle. It was found that, as in the rabbit, fibres terminate mainly in the plexiform layer, although some penetrate into the deeper layers of the tubercle and in a few instances into the superficial islands of Calleja. Rose (1927a and b), on the basis of differences in cyto-architecture, divided the olfactory tubercle into rostral, middle, and caudal regions, Tol 1, Tol 2, and Tol 3. According to his detailed comparative studies, the rostral part, although well-developed in lower mammals, is rudimentary in structure in the monkey and in Man. In the rabbit, his area Tol 1 is more extensive and corresponds closely with the part receiving olfactory fibres, as determined by Le Gros Clark and Meyer. In the present investigation we have found that Rose's delimitation of the rudimentary area Tol 1 in the monkey again coincides almost precisely with our definition of the area in which olfactory fibres terminate. An interesting demonstration of the close correspondence between cyto-architecture and function is thus afforded for the olfactory area of the tubercle. From the reduced extent of this area it is evident that in the monkey the tubercle participates in olfaction only to a limited degree, and its quite considerable size in this species is thus evidently due to the relative enlargement of the non-olfactory areas.

Amygdaloid Complex.—Johnston (1923), on the basis of differences which he observed in comparative studies, divided the amygdaloid complex into a cortico-medial and a baso-lateral group. Subsequent workers have followed his classification, recognizing in addition an anterior amygdaloid area and a cortico-amygdaloid transition area. In their description of the amygdaloid complex in the human brain, Crosby and Humphrey (1941) state that the baso-lateral group of nuclei is more highly differentiated than in macrosmatic mammals, while the cortico-medial group (in particular the nucleus of the lateral olfactory tract and the medial and central

amygdaloid nuclei) is much reduced. This observation suggested to these authors a relationship in function and in degree of development between the cortico-medial group and the main olfactory centres.

In rabbit experiments, Le Gros Clark and Meyer (1947) showed that the cortico-medial group of the amygdaloid complex receives direct fibres from the olfactory bulb, but the baso-lateral group does not, a fact which demonstrates that Johnston's two subdivisions are functionally as well as phylogenetically distinct. After sectioning of the olfactory peduncle in the monkey, the pattern of distribution of olfactory fibres to the amygdaloid complex is essentially the same as in the rabbit, although the position of the areas which are wholly or partly olfactory in function is somewhat altered and they are relatively much reduced in size. In lower mammals the superficially placed nuclei of the cortico-medial group, often termed the peri-amygdaloid area, lie on the basal surface of the telencephalon and constitute, together with the prepiriform cortex which lies dorsolateral to the peri-amygdaloid region, the anterior part of the piriform lobe. With the enlargement of the neocortex in monkey and man the peri-amygdaloid region is moved forward in a dorso-medial direction and comes to lie on the dorsal surface of the temporal lobe, where it forms the gyrus semilunaris. Thus the prepiriform cortex now lies anterior to the peri-amygdaloid area and the sulcus semiannularis separates the two regions.

Most of the fibres of the lateral olfactory tract end anterior to the peri-amygdaloid area, and, in the monkey, only a small component passes backwards in the entorhinal sulcus to spread over and terminate in the peri-amygdaloid region.* After sectioning the olfactory peduncle in *Macaca* and *Papio* degeneration of this component of the lateral olfactory tract shows that its fibres are distributed mainly to the antero-medial part of the peri-amygdaloid nuclei. Olfactory fibres penetrate quite deeply into the medial amygdaloid nucleus, apparently terminating in contact with the bodies of the neurones of which it is composed. The nucleus of the lateral olfactory tract consists of two parts, as has been described for man, the rabbit, and the bat. Fascicles of degenerating fibres detach themselves from the olfactory fasciculi in the superficial layer of the peri-amygdaloid region to enter this nucleus and terminate on its nerve cells. Part of the nucleus lies amongst the olfactory fibres which pass on in the superficial layer (Fig. 10). The cortical amygdaloid nucleus is more highly differentiated in the monkey and in Man than in lower mammals and has been regarded by several authors as true cortex. According to the evidence presented here it receives fewer olfactory fibres than the medial amygdaloid nucleus or the nucleus lateral olfactory tract. Degenerating fibres and terminals are localized in the superficial and plexiform layer of the cortical nucleus, which indicates that synaptic contact is axodendritic, as in the prepiriform cortex.

Lauer (1945), in describing the amygdaloid nucleus in the brain of *Macaca*, places the cortico-amygdaloid transition area in the lateral part of the amygdaloid fissure between the peri-amygdaloid region and the entorhinal area (which is labelled piriform cortex in his diagrams). We could not certainly trace any olfactory fibres to this region. In the material at our disposal another group of nerve cells could be identified, lying in the antero-medial part of the semi-circular amygdaloid fissure (or semi-annular sulcus). It forms a transition area between the prepiriform cortex and the peri-amygdaloid region (Fig. 10) and is also in cellular continuity with the anterior part of the basal accessory amygdaloid nucleus. A substantial component of olfactory fibres was traced into this area. It is possible that this is the antero-medial part of a transition area which lies under the entire semi-annular sulcus and is continuous with the cortico-amygdaloid transition area described by Lauer in the macaque and also by Crosby and Humphrey in the human brain. Only the antero-medial part of it, however, receives olfactory impulses and perhaps functions, as Crosby and Humphrey suggested, as a distributing centre for olfactory impulses to the baso-lateral group.

Olfactory fibres are distributed to the two remaining nuclei of the cortico-medial group, namely the bed nucleus of the stria terminalis and the central amygdaloid nucleus, by way of the anterior limb of the anterior commissure. These two nuclei are directly continuous, the bed nucleus of the stria terminalis extending from the amygdaloid region upwards and forwards as a thin band over the internal capsule and then reaching downwards into the medial preoptic region, where it attains a considerable size (as Papez and Aronson, 1934, point out). After transection of the olfactory peduncle degeneration in both these nuclei is bilateral. In the monkey, however, a substantial part of the fine fibre plexus remains intact, whereas in the rabbit there is almost complete degeneration of the terminal plexus after excision of the olfactory bulb. The different results in the two species suggest that in the monkey the central amygdaloid nucleus and the bed nucleus of the stria terminalis are not predominantly olfactory in function, as they

* Rose (1927) did not recognize in his cyto-architectural studies that the lateral olfactory tract together with the prepiriform cortex has been pushed further forward than the amygdaloid region for he states that the entire tract terminates in the area peri-amygdalaris.

evidently are in the rabbit. The regression of the olfactory component of the anterior commissure in primates, which has been emphasized by Fox and others (1948) in an experimental Marchi study, supports this inference. Nevertheless, our material provides convincing evidence that even in primates the bed nucleus of the stria terminalis (particularly that part which lies in the preoptic region) and the central amygdaloid nucleus form a definite part of the olfactory system. Physiological evidence in accordance with this observation has been obtained in cats by Hess and Müller (1946), who report centrally induced sniffing responses after electrical stimulation of the nucleus of the stria terminalis and other related areas.

Prepiriform Cortex.—The great majority of fibres of the lateral olfactory tract terminate in the superficial layers of the prepiriform cortex. The method which we have employed has enabled us to map out precisely the extent of the degenerating olfactory terminals, and in Fig. 17 their distribution is indicated on the surface of the brain. This prepiriform area, which represents the primary olfactory cortex, has never been clearly defined in primates; previous investigators have failed to homologize it with the relatively much larger region it occupies in lower mammals, even though the cyto-architecture is typical. Phylogenetically, the folding over and displacement of the so-called rhinencephalon in a fronto-medial direction begins in lower primates with the development of the neocortex of the temporal lobe. The posterior part of the hippocampal gyrus (the entorhinal area) is also gradually moved forward and the prepiriform cortex (together with the terminal arborizations of the lateral olfactory tract) is folded over the frontal lobe and displaced in front of the uncus. In the macaque and baboon, the primary olfactory cortex thus lies on the dorsal surface of the temporal lobe. It occupies the anterior part of the hippocampal gyrus (which corresponds to the gyrus ambiens in man), and it is clearly separated from the neocortex of the temporal pole by the rhinal sulcus, while the sulcus semi-annularis delimits it from the amygdaloid complex of the gyrus semilunaris. The temporal prepiriform cortex passes over without any external markings into the entorhinal area, whereas in man a sulcus separates the gyrus ambiens from the hippocampal gyrus proper. In normal silver preparations the first layer of the temporal prepiriform cortex consists of a dense mass of fine fibres turned inwards towards the pyramidal cell layer. These fibres degenerate after sectioning of the olfactory peduncle, and, since signs of terminal degeneration are rarely seen within the pyramidal cell layer, it is concluded that synaptic contact is axo-dendritic. No olfactory fibres reach the isocortex of the insula directly. Beck (1934), in a description of the myelo-architecture of the dorsal cortex of the temporal pole in the monkey, describes the first layer of this region as extraordinarily thick, increasing in thickness antero-posteriorly (that is to say as it approaches the olfactory tract). His description corresponds to our findings, but he fails to relate the fibre layer he describes to the olfactory tract and does not appear to realize that these fibres are its terminal arborizations. The dense superficial fibre layer coincides with the appearance of typical prepiriform cortex, the cyto-architecture of which in the macaque is closely homologous with that of lower mammals. It is characterized by its well-defined second layer of closely packed pyramidal cells which are sometimes grouped into islets. The series of Nissl-stained sections through this region of allocortex (shown in Figs. 5 to 10) is representative of this area in the macaque.

The area of prepiriform cortex which lies on the orbital surface of the frontal lobe is very restricted in primates; it appears somewhat behind the rostral limits of the olfactory tubercle and receives relatively few olfactory fibres. This area occupies the same general position as does the corresponding area in the rabbit and mouse.

Rose (1927 a and b) has made an extensive study of the cyto-architecture of the allocortex in lower mammals and in primates. According to his interpretation the prepiriform cortex in the monkey (*Cynocephalus hamadryas*) is restricted to the basal surface of the frontal lobe (his prepyriform areas 1, 2, and 3) with the exception of a very small part of prepyriform 3, which overlaps a little on to the temporal lobe. The temporal prepiriform or primary olfactory area, localized from our experimental material, is included in his diagrams of the monkey in the entorhinal region (the anterior part of areas eα, eβ, eγ). However, his photomicrograph of these areas has been taken at the level of the amygdaloid nucleus, where the cortex is different from the anterior part and clearly belongs to the non-olfactory entorhinal area. In lower mammals, also, Rose has not distinguished clearly between the prepiriform cortex, the entorhinal area, and the peri-amygdaloid region, in some instances regarding the whole olfactory cortex of the piriform lobe as peri-amygdaloid area (lemur, dog), in others as part of the entorhinal area (mouse). In a later comparative study on the insular cortex (1928) Rose includes the temporal prepiriform cortex of the monkey in the agranular cortex of the insula (ai 9, ai 10). The cyto-architecture is described in

detail by him and confirms our own evidence; he makes no suggestion, however, that this area is to be regarded as prepiriform cortex. He does indicate that the entire agranular insular cortex might have functions related to smell; but, in his definition of agranular insular cortex, areas are included which have certainly no connexion with olfactory fibres. In Brodmann's cyto-architectural charts of lower mammals, the prepiriform cortex (together with the olfactory tubercle and peri-amygdaloid region) is included in area 51. In his maps of the lemur and monkey cortex this region is unlabelled. Area 34 in Brodmann's chart of the human cortex appears to be equivalent to the prepiriform cortex, together perhaps with the anterior part of his area 28 (entorhinal area). There is, as yet, no precise definition of the extent of the cortical projection area of the olfactory tract for the human brain. Brodal's (1947) attempt to transfer the findings in animals to the brain of man is based mainly on the descriptions and figures of Rose, but it is doubtful whether the functional properties of any cortical fields can be defined solely by their architectonic features, without reference to their connexions. Lauer (1945) includes the prepiriform area of *Macaca* in his lateral part of the anterior olfactory nucleus.

Physiological evidence supports the view that the primary olfactory area in monkeys is located in the anterior extremity of the hippocampal gyrus. As early as 1886 Ferrier reported that electrical stimulation of this area in monkeys (and also the corresponding region in dogs, cats, and rabbits) resulted in a peculiar torsion of the lip and nostril on the same side. This reaction was the same as that induced by direct application of strong or disagreeable odours to the nostril and was regarded as "evidently the outward or associated expression of excited olfactory sensation." In lower mammals it has been found by several investigators (for example, by Fox and others, 1944) that stimulation of the olfactory bulb is followed by conspicuous potential changes in the anterior piriform cortex. Some human cases provide further evidence that the primary olfactory cortex lies in the anterior hippocampal gyrus. Thus, Uyematsu (1921) has described two brains with unilateral destruction of the olfactory peduncle in which the resulting cellular atrophy was confined to the piriform area, "lateral to the gyrus circumambiens and anterior to the uncus proper," and this area appears to correspond to the temporal prepiriform cortex as delimited by us in the monkey brain.

Summary

1. The central connexions of the olfactory tracts have been determined experimentally in three macaque monkeys and two Guinea baboons by following with a silver method the degeneration of fibres and terminals which result from unilateral transection of the olfactory peduncle.

2. It was found that the lateral olfactory tract terminates mainly on the dorsal surface of the temporal lobe, in the superficial layer of the prepiriform cortex which forms the anterior part of the hippocampal gyrus. Some fibres of the tract terminate in the prepiriform cortex lying on the orbital surface of the frontal lobe (which is very restricted in primates), in the olfactory tubercle, and in the peri-amygdaloid area. The primary olfactory areas have been mapped out on the surface of the macaque brain (Fig. 17).

3. Only the cortico-medial group of nuclei of the amygdaloid complex receives fibres from the olfactory tracts, not the baso-lateral group. Olfactory fibres are bilaterally distributed by way of the anterior limb of the anterior commissure to the nucleus of the stria terminalis (the main part of which lies in the preoptic region), and to the central amygdaloid nucleus.

4. No olfactory fibres could be traced to the septum, the entorhinal area, or any part of the hippocampal formation in the lateral ventricle. A few fibres from the tract reach the superficial layer of the anterior hippocampal nucleus.

5. It is evident that in primates the general pattern of distribution of olfactory fibres is similar to that in lower mammals, although the primary olfactory areas have been displaced and have become relatively much reduced in the course of evolution.

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DEGENERATION OF THE GRANULAR LAYER OF THE CEREBELLUM

BY

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The following investigation was initiated by the observation by one of us (Meyer, 1944), of a selective degeneration of the granular layer of the cerebellum in a case of a Wernicke syndrome associated with carcinoma of the stomach. The possible relation to one or other type of nutritional deficiency (not necessarily that of vitamin B_1) was discussed, but no consideration was given to the fact that there might be a more direct causal relation to the carcinoma. There has been a fair number of reports on cases of visceral carcinoma in which clinical and/or pathological signs of cerebellar degeneration (not associated with secondary deposits) were discovered. (Lhermitte, 1922 ; Casper, 1929 ; Scherer, 1933 ; Parker and Kernohan, 1933 ; Greenfield, 1934 ; Kennard, 1935 ; Zülch, 1936 ; Courville and Friedman, 1940 ; Alessi, 1940 ; Buchanan and others, 1947.) A causal relation between the carcinoma and the cerebellar lesion was by no means assumed in all of these communications. Indeed in the cases of Courville and Friedman, and Buchanan and others, it was expressly rejected in view of the clinical history. In the opinion of Brouwer and Biemond (1938), however, the rapid development of a cerebellar lesion in cases of carcinoma was such as to suggest the influence of a carcino-toxic agent. The granular layer, if involved, was not always selectively affected in their cases, but in the most important observations published on this subject by Bertrand and Godet-Guillain (1942) the granular layer was indeed selectively involved. In fourteen out of sixteen cases of visceral carcinomata these authors described varying stages of degeneration of the granular layer, betraying itself even on macroscopic inspection by an appearance they termed " glacé." These cerebellar changes were most marked in the dorsal part of the vermis and were usually accompanied by degenerative signs in the inferior olives, particularly in their dorsal portion. This predilection for the dorsal aspects of the cerebellum recalls that seen in the delayed type of cerebellar atrophy (Foix and others, 1922), more recently known as parenchymatous cerebellar atrophy. This relationship, which is important in view of the usual age period of carcinoma, has in fact been discussed in the literature (Casper, 1929 ; Brouwer and Biemond, 1938). The latter authors concluded, however, that there was no relationship between the two conditions, as they found a diffuse distribution of the cerebellar changes in the carcinoma cases, as compared with the more focal distribution in the delayed atrophy. In the cases described by Bertrand and Godet-Guillain no clinical cerebellar signs were observed, and the authors considered, therefore, that the cerebellar lesions had developed rapidly during the terminal cachectic phase of the carcinomatous process.

Apart from the association with visceral carcinomata, a selective degeneration of the granular layer of the cerebellum has been attributed to a variety of causes. One of the first descriptions of the condition was given by Bielschowsky (1920) in infantile, late infantile, and juvenile cases of amaurotic idiocy. Since his description, this " cerebellopetal " type of degeneration has been regarded by many as the predominant type of cerebellar involvement in cerebro-macular degeneration. Norman (1940) showed that selective degeneration of the granular layer may also occur in mental defectives other than those suffering from amaurotic idiocy. Both his patients died from pulmonary tuberculosis, complicated in one by a terminal tuberculous enteritis. In this patient the terminal disease clearly preceded the onset of cerebellar signs. We mention this relationship because wasting diseases and, in particular, severe gastro-enteritis have been given some attention, especially in the older literature (Murri, 1900 ; Rossi, 1907 ; Archambault, 1918). Senile cachexia and malnutrition have also been discussed, particularly in relation to the delayed cerebellar atrophies of old age (Courville and Friedman, 1940). Diabetes mellitus has been noted in the literature as a possible cause. Shinosaki (1926), describing cerebellar changes in a case of severe congenital diabetes, clearly illustrated a selective degeneration of the granular layer. In keeping with views

current at that time he discussed the possible causation of diabetes by lesions of the vermis, particularly of the uvula. One of Winkelman's (1943) cases of granular layer degeneration was a diabetic who died following an operation for acute gangrene of the intestinal tract and hæmorrhagic gastritis. The most important investigation in this field was carried out by Bertrand and Tiffenau (1942), who found a selective degeneration of the granules in the dorsal part of the cerebellum in five cases dying in diabetic coma, and in all cases the appearance and distribution were similar.

A more or less selective degeneration of the granular layer has also been described after prolonged experimental carbon-monoxide poisoning (Ferraro and Morrison, 1928), and in various toxi-infectious conditions, including lead, carbon monoxide, and histamine poisoning, inanition, and septicæmia (Williams, 1934). Two papers describing more recent experimental work require special mention. Upners (1939) administered thiophen ($C_4 H_4S$) to dogs in small doses over long periods, and found a selective action on the granular layer, resulting in its degeneration, usually combined with pathological changes in the quadrigeminal region resembling those seen in Wernicke's syndrome. In all the animals frequent vomiting and anorexia were conspicuous. Likewise the administration of methyl mercury compounds to rats and a monkey (Hunter and others, 1940) resulted in rapid loss of weight, followed by specific nervous disturbances. In the rats on which multiple observations were possible the peripheral nerves and posterior spinal roots were affected first, the posterior columns and granular layer of the middle lobes of the cerebellum later.

This review of the literature, though probably by no means complete, demonstrates that certain metabolic factors may be of importance in the pathogenesis, classification, and ætiology of certain cerebellar degenerations. It was for this reason that we considered a further investigation of the problem was justified.

Material

Our material consists of (1) fourteen cases of visceral carcinoma with or without metastases in brain and other organs. Eight of these showed a degeneration of the granular layer. The negative cases comprised patients suffering from a variety of visceral carcinomata (of rectum, stomach, œsophagus, gall bladder, bronchus, prostate).

(2) Six cases dying in diabetic or hypoglycæmic coma. Of these two were definite hyperglycæmic fatalities; in neither was there any cerebellar affection, although in one a complete olivary degeneration, and severe acute cell changes (lysis) most marked in the third layer of the cerebral cortex and of the parvo-cellular elements of the corpus striatum were present, similar to the changes described by Bertrand and Tiffenau (1942). Both cases are excluded from full description in this paper; the remaining four include a case of doubtful hyperglycæmic coma, a diabetic dying from irreversible hypoglycæmia, and two schizophrenics with hypoglycæmia induced for therapeutic purposes and dying in irreversible coma. The last three cases of proved hypoglycæmia were found in a total material of nine cases of fatal hypoglycæmia.

(3) Four cases of amaurotic idiocy, all showing a degeneration of the granular layer.

In all cases investigated for this paper a full histological investigation of the brain has been made by the usual methods.

Group I: Visceral Carcinoma

Case 1.—A man aged 62 years was the subject of a previous report by one of us (Meyer, 1944). He died after an illness of approximately twelve months' duration, the clinical diagnosis being gastric carcinoma. This was confirmed at autopsy.

Autopsy Findings.—Macroscopically there was some thickening of the leptomeninges at the base of the brain, particularly within the interpeduncular space. In the cerebellum there was no general reduction in size, but a glassy appearance was noticed in what would correspond to the granular layer. Histologically, there were changes in the hypothalamus characteristic of Wernicke's encephalopathy. These changes, however, were atypical in so far as the glio-mesodermal proliferation was more conspicuous in the anterior part of the hypothalamus than in the mammillary bodies, which showed signs of a very recent affection only.

In the cerebellum a selective degeneration of the granular layer was present. In Nissl preparations the Purkinje-cell layer contrasted prominently with the granular layer, the granules failing to stain with cresyl violet (Fig. 1). With high-power magnification, instead of the darkly-stained nuclei of the granules, with their well-defined chromatin, only the shadows of severely deformed nuclei in varying degrees of disintegration were to be seen. The cytoplasm, normally not well seen, appeared to merge with that of adjacent cells, thus producing what has aptly been termed " conglutination." This process was found throughout the granular layer, but was not quite so advanced in the ventromedial sector as in the remaining sectors of the cerebellum.

In myelin preparations also, the ventral and especially ventromedial areas showed a better staining reaction in the granular layer, particularly near the summit of lobules. This was due to nuclear staining, which was in varying degrees deficient in the other parts of the granular layer. The translucent appearance was not due to a diminution of the myelinated fibres, which, though conspicuously beaded, were seen to traverse

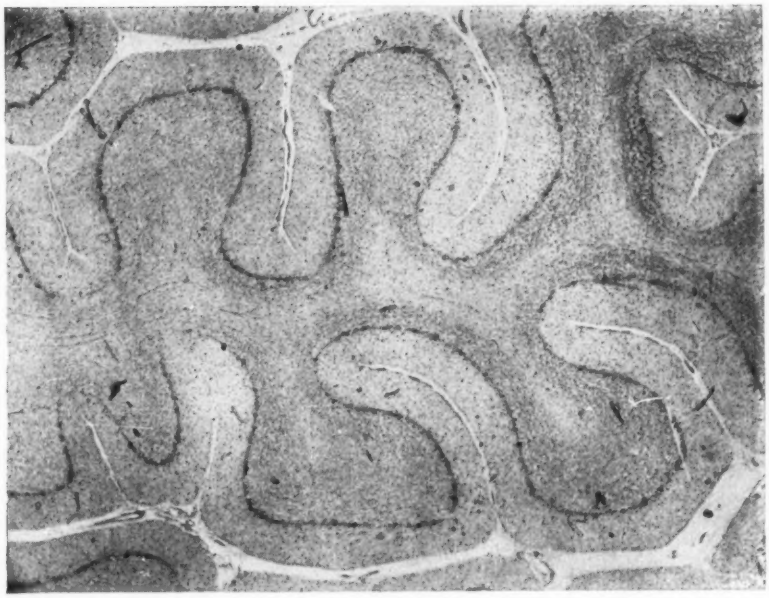


FIG. 1.—Diffuse degeneration of granular layer in a case of gastric carcinoma (Case 1). Nissl, ×18.

this region in normal numbers. Bielschowsky silver preparations disclosed normal basket cells and processes, with no diminution in the fibres of the granular layer. The Bergmann glia contained an excess of lipoids, and much fat was also seen in the glia cells and mesodermal elements of the granular layer, and to a lesser degree in the white matter. No appreciable microglial proliferation was seen in Penfield preparations, nor was any fibrous gliosis revealed by the Holzer technique.

The dentate nucleus was little affected, save for an excess of lipofuscin in nerve cells and some degree of patchy glial proliferation. In the inferior olives it was immediately apparent with low magnification that there was a diminution of nerve cells, most marked in the dorsomedial corner of the nucleus. High-power inspection revealed that all nerve cells showed some pigment degeneration, but that in the dorsomedial portion the cells had become opaque discs, with the nuclei either dark and shrunken or breaking up into granules. In this region there was considerable gliomesodermal reaction, and in Holzer preparations a moderate diffuse glial fibrosis was seen. No demyelination was noted.

The blood vessels of brain and meninges showed moderate fibrosis, and in the cerebral white matter a rarefaction of tissue in close vicinity to the thickened vessels had produced the picture of small " criblures." Apart from this change, however, no significant abnormality was present in the cerebral hemispheres.

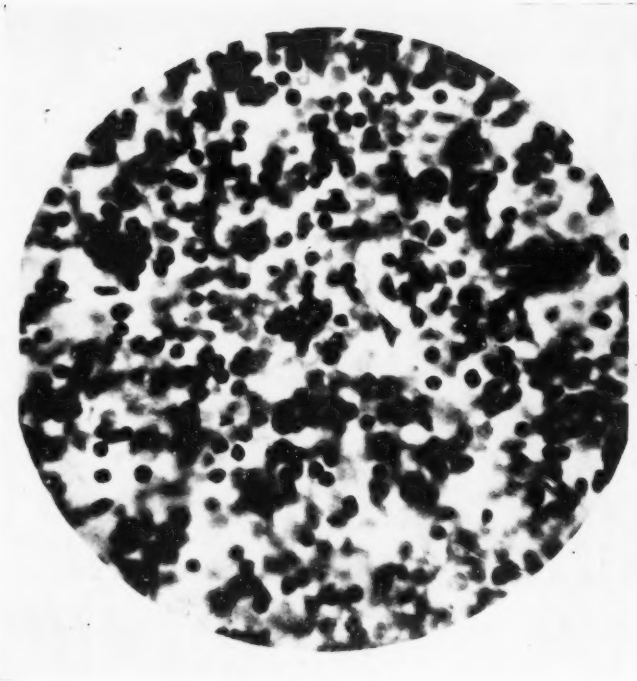
Case 2.—A man aged 67 was admitted to King's College Hospital with a six weeks' history of epigastric pain and loss of weight. His condition rapidly deteriorated, and he died two weeks after admission. The diagnosis was of carcinoma of the bladder, with metastatic deposits in the liver.

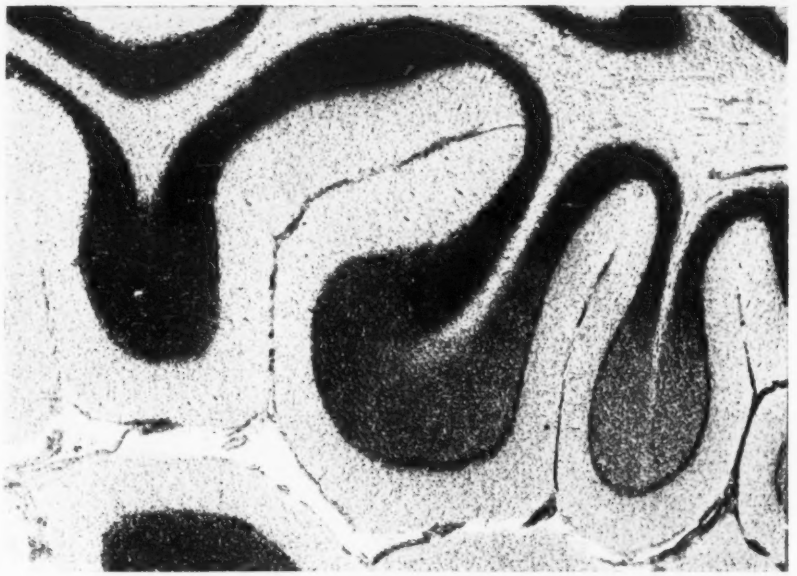
Autopsy Findings.—A squamous-celled carcinoma of the bladder, with secondary deposits in the liver and the abdominal lymph glands, was discovered at necropsy.

The brain weighed 1,440 g. The meninges were opaque over the whole of the vertex, and there was slight generalized convolutional atrophy. Apart from these findings no gross abnormality was noted.

Histologically, the only pathological findings of importance were confined to the cerebellum. In Nissl-stained sections the Purkinje cell layer and the Bergmann layer were well preserved. The granular layer, however, showed varying degrees of degenerative change. Some folia were normal in appearance, whilst in others an almost complete necrosis of the granular layer had occurred. Even the granules less severely affected showed some loss of configuration of the nuclear chromatin, the nuclear membrane being no longer visible and the shape no longer quite rounded. Many cells, however, had almost entirely lost their affinity for cresyl violet, a more or less homogeneous and markedly deformed disk alone remaining. Still more advanced degeneration was indicated by faint shadows of nuclear débris. The Golgi cells of this layer were well preserved, standing out in marked relief amidst the areas of necrosis. In myelin preparations the granular layer was only lightly stained, but did not show the extreme " translucency " of other cases in this series. There was no loss of myelinated fibres, the " light " staining resulting from the poorly stained cell bodies. Silver preparations also showed no loss of fibres in the granular layer, although beading was present. Basket cells and fibres were well preserved. The molecular layer showed no abnormality.

The dentate nucleus was intact, the nerve cells showing





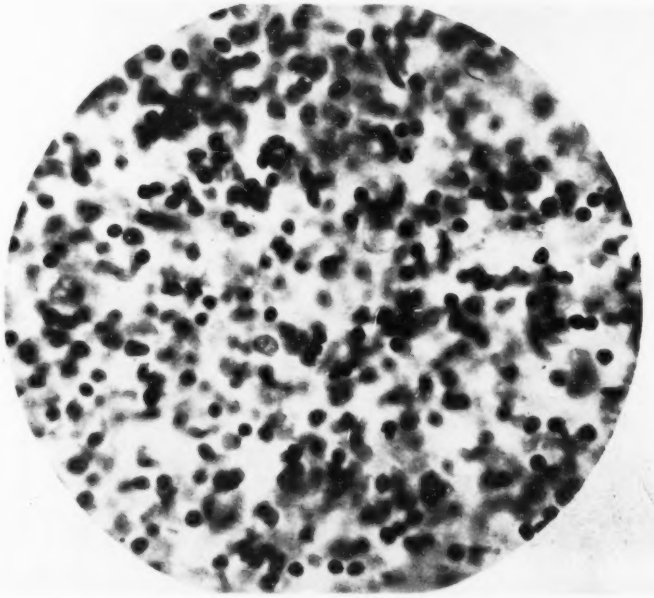
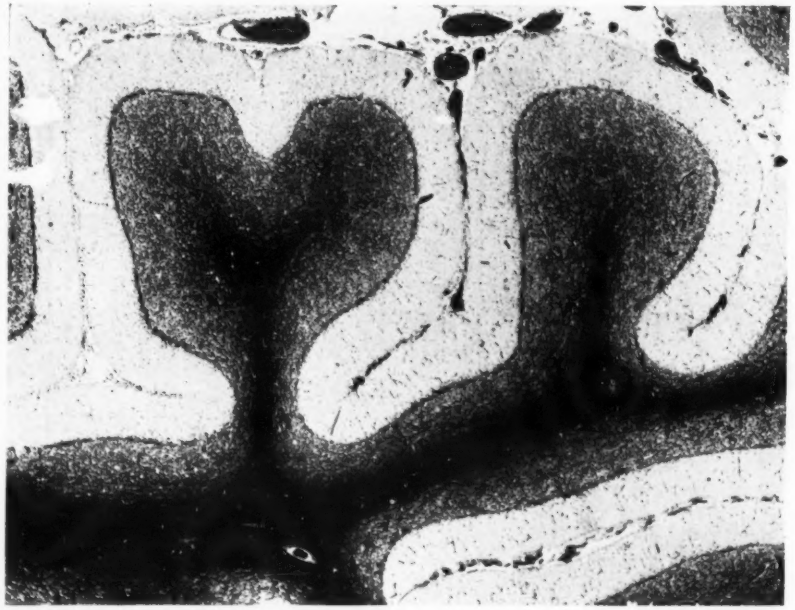
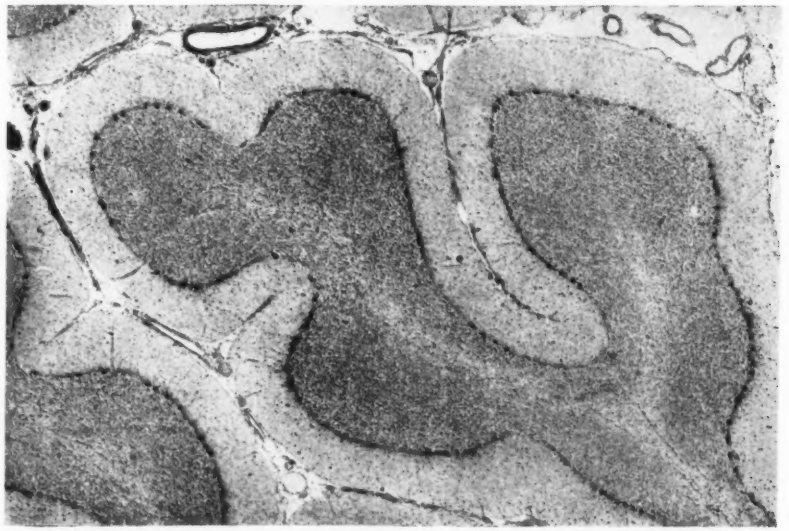


FIG. 2 (above).—Granular layer showing necrosis, deformation, and clumping of the granules, in a case of carcinoma of gall bladder (Case 3). Nissl, ×550.

FIG. 3 (top right).—Focal necrosis of granules at summits of folia in a case of carcinoma of bladder (Case 4). Nissl, ×22.

FIG. 4 (lower right) .—Necrosis of granular layer in a case of hypoglycæmic coma (Case 12). Nissl, ×550.





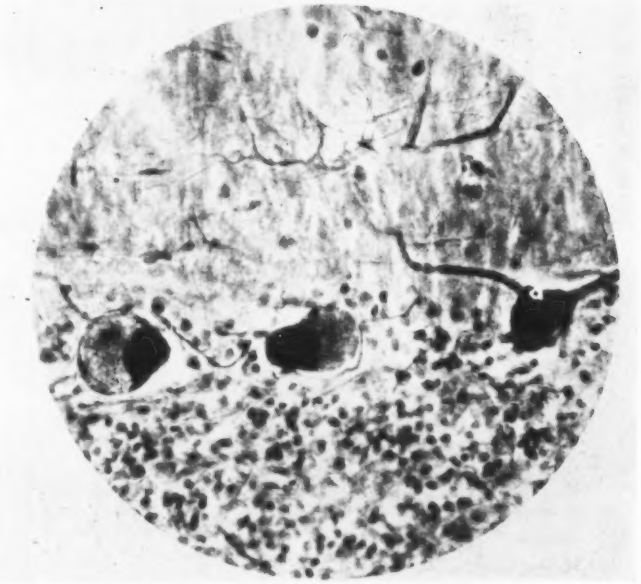


FIG. 5 (above).—Degeneration of granular layer in a case of amaurotic idiocy (Case 14). Heidenhain, ×22.

FIG. 6 (top right).—Degeneration of granular layer in a case of amaurotic idiocy (Case 14). Nissl, ×22.

FIG. 7 (lower right).—Absence of basket cells and fibres in a case of amaurotic idiocy (Case 14). Bielschowsky, ×300.

a lipofuscin change commensurate with the age of the patient.

The olives showed a general diminution in the number of nerve cells, all of which showed extreme pigment atrophy.

In Holzer preparations there was gliosis in the cerebellar white matter (but not in the cortex) and in the region of both inferior olives.

There was no abnormality in the remainder of the brain or in its blood vessels.

The remaining six cases showed substantially similar appearances and will not be described in detail. The relevant data appear in Table I.

Group II : Hypoglycæmic and Diabetic Coma

In this group we had four cases. Case 12 is described below in detail, and the relevant data for the whole group are abstracted in Table II.

Case 12.—A woman aged 30, a diabetic of 8 years' duration, was admitted to King's College Hospital in hypoglycæmic coma. In spite of vigorous treatment, she died after a period of coma lasting seventeen days.

Autopsy Findings.—Widespread cavitation of the Swiss-cheese type was seen within the cerebral white matter and the basal ganglia. This was due to a profuse growth of the gas-forming *Cl. Welchii*, which was found

TABLE I

GRANULAR LAYER DEGENERATION ASSOCIATED WITH VISCERAL CARCINOMATA

Case	Age at death	Duration of illness (mths.)	Pathological diagnosis	Cachexia	Secondary deposits	Complications	Granular layer degeneration	Inferior olive	Other C.N.S. abnormalities
1	62	12	Carcinoma of stomach	+	—	Wernicke's syndrome; mania	Generalized, but more marked in dorsal cerebellum (Fig. 1)	Severe changes; outfall of nerve cells in dorso-medial portion of olivary nucleus	Moderate fibrosis of cerebral and meningeal blood vessels, producing the appearance of small "criblures" in the cerebral white matter.
2	67	6	Carcinoma of bladder	+	Hepatic	—	Patchy	Slight general nerve-cell reduction	Nil
3	60	3	Carcinoma of gall-bladder	+	Hepatic	—	Patchy (Fig. 2)	Severe changes; almost complete disappearance of nerve cells	Nil
4	66	8	Carcinoma of bladder	+	—	Oral signs of vitamin B deficiency	Patchy (Fig. 3)	Slight general nerve-cell reduction	Lipofuscin change in nerve cells of cerebral cortex, subcortical grey masses, and brain stem nuclei. Severe pigment atrophy of cells of dentate nucleus. Moderate gliosis in region of dentate nucleus and in cerebellar white matter, and in all marginal zones.
5	66	12	Carcinoma of pancreas	+	Hepatic	Glycosuria	Generalized; some reduction in number of Purkinje cells	Normal	Nil
6	51	6	Carcinoma of breast	+	Cerebral	Mentally defective since birth	Generalized	Some general diminution of nerve cells, with rarefaction of dorsal flexure	Nil
7	53	6	Carcinoma of bronchus	+	Cerebral	"Korsakow's psychosis"	Generalized	Slight general nerve-cell reduction	Nil
8	75	Unknown	Carcinoma of stomach	+	—	—	Generalized	Normal	General pigment atrophy, with some reduction of the nerve cells of the cerebral cortex. *État criblé* in putamen and pallidum. Fibrosis of cerebral vessels with varying degrees of cerebral atheroma.

TABLE II

DEGENERATION OF THE GRANULAR LAYER ASSOCIATED WITH HYPOGLYCÆMIC AND DIABETIC COMA

Case	Age at death	Duration of illness	Clinical diagnosis	Cachexia	Complications	Granular layer degeneration	Olivary nuclei	Other C.N.S. abnormalities
9	21	Coma—60 hours	Hypoglycæmic coma; schizophrenia	—	—	Diffuse	Some generalized reduction in nerve cells	Widespread severe necrosis in frontal, parietal, and temporal cortex, and in Sommer sector and endfolium of the Ammonshorn. Dentate nucleus—general cellular reduction with pigment atrophy of those nerve cells remaining.
10	17	Coma—36 hours	Hypoglycæmic coma; schizophrenia	—	—	Diffuse; Purkinje cells showed acute cell change	No abnormality	Foci of cellular necrosis in the fifth and sixth layers of the frontal, parietal, and temporal cortex. The Sommer sector and endfolium of Ammonshorn were almost devoid of nerve cells.
11	10	Coma—? duration	? Hypoglycæmic coma; ? hyperglycæmic coma; diabetes mellitus	—	Epileptic attacks since age 6	Diffuse	No abnormality	Sector necrosis of Ammonshorn, marginal gliosis of the cerebral cortex, and some perivascular and diffuse gliosis within the cerebral white matter.
12	30	Coma—17 days	Hypoglycæmic coma; diabetes mellitus	—	—	Diffuse (Fig. 4)	No abnormality	See full case report.

inside the blood vessels and the adjacent tissues. There was no inflammatory reaction to the bacillary invasion, so that it must have occurred immediately before, or just after, death. Histologically there was widespread loss of nerve cells in the cerebral hemispheres, with a corresponding microglial and neuroglial reaction. These pathological findings have been reported in full elsewhere (Lawrence and others, 1942) and were considered to be the result of the prolonged cerebral anoxia.

The cerebellum showed a typical granular layer degeneration which had not been noticed at the time of the earlier publication. In Nissl preparations the Purkinje cells were well stained and in no way abnormal. The granules, however, were thinned out, many cells showing complete disappearance of their nuclei, and staining homogeneously with basic dyes (Fig. 4). This change in the granular layer was present throughout the cerebellar cortex. In myelin stains the pale grey appearance of this layer contrasted with the darkly staining layer of Bergmann glia. Silver impregnation showed preservation of basket cells and fibres, with no diminution in the fibres of the granular layer. In Scharlach R sections some increase in lipoids could be seen in the histiocytic and microglial cells, in both the Bergmann and granular layers. No fibrous gliosis was observed with the Holzer technique in any of the cerebellar layers.

The dentate nucleus and the olives of this brain were not available.

TABLE III

GRANULAR LAYER DEGENERATION IN AMAUROTIC IDIOCY

Case	Age at death	Duration of illness	Clinical diagnosis	Cachexia	Complications	Granular layer degeneration	Olivary nuclei	Other C.N.S. abnormalities
13	19	Several years	Amaurotic family idiocy	+	Epileptic fits	Diffuse; gliosis present	Not available	"Ballooning" of nerve cells throughout the brain characteristic of amaurotic idiocy.
14	15	Several years	Amaurotic family idiocy	+	Hypostatic pneumonia; epileptic fits	Diffuse (Figs. 5, 6). Gliosis present	Severely affected, loss of nerve cells particularly in dorsomedial portion of nucleus	"Ballooning" of nerve cells throughout the brain characteristic of amaurotic idiocy.
15	?	Several years	Amaurotic family idiocy	+	No clinical notes available	Diffuse; gliosis present	No abnormality	"Ballooning" of nerve cells throughout the brain characteristic of amaurotic idiocy.
16	19	Several years	Amaurotic family idiocy	+	No clinical notes available	Patchy; severe outfall of Purkinje cells; gliosis present	Not available	"Ballooning" of nerve cells throughout the brain characteristic of amaurotic idiocy.

Group III : Amaurotic Idiocy

Again four cases were available for examination. Case 14 is described in full, and Table III summarises the remainder.

Case 14.—A boy was admitted to hospital at the age of 11 years. He was blind and suffered from epileptic attacks. He deteriorated slowly for four years, becoming bedridden and incontinent. He finally died at the age of 15, as a result of hypostatic pneumonia.

Autopsy Findings.—No macroscopic abnormality was recorded in the brain. Histological examination disclosed ballooning and lipoid infiltration in the nerve cells throughout the nervous system. In the cerebellum a granular layer degeneration was present. With myelin techniques the characteristic "lightening" of the granular layer was clearly demonstrated (Fig. 5). In Nissl sections the Purkinje cells, though globular in shape and infiltrated with lipoid material, stained well, and showed no diminution in number. In contrast, hardly a normal granule cell could be found throughout the whole cerebellar cortex (Fig. 6). The Golgi cells of this layer, however, had survived intact. The Bergmann glia was not proliferated. In Holzer preparations a slight fibrous gliosis was seen in the white matter of the lobules and around the dentate nucleus. In the granular and molecular layers there was a considerable astrocytic gliosis.

Bielschowsky silver preparations showed almost complete disappearance of basket cells and their fibres (Fig. 7). The radial fibres of the molecular layer were absent. The dendritic processes of the Purkinje cells and their axones showed no abnormality. In the granular layer there was great diminution in the nerve fibres.

The cells of the dentate nucleus were not diminished in number, but showed well marked "ballooning" and lipoid infiltration.

In the medulla the inferior olives proved to be severely affected. With low magnification a general diminution in cells was at once apparent, whilst in the dorsomedial portion of the nucleus hardly a nerve cell remained. With higher magnification the remaining cells showed much lipoid infiltration, with distortion of their cell bodies. Holzer preparations disclosed a fibrous gliosis in the region of both inferior olives.

Discussion

In the first place it should be emphasized that we have excluded any case in which the pathological signs of degenerative changes in the granular cells were questionable. Faint staining with the Nissl method alone, without the phenomena of conglutination, deformation, or other nuclear or cytoplasmic signs of cell degeneration, was never considered as pathognomonic, as this may be a staining artefact, particularly in brains which have been long in formalin. As it happens, most of our material was embedded soon after fixation in formalin was completed. Comparison with other staining methods, especially myelin stains, was helpful in the evaluation of the changes.

Even after the application of such rigid criteria, our results constitute an impressive confirmation of the claims of Bertrand and his associates, particularly with regard to the carcinoma group, in which eight out of fourteen cases showed this type of degeneration. In the diabetic and hypoglycæmic group our results differ from those of Bertrand and his associates, for in two cases of undoubted diabetic coma the granular layer was normal. In three of the remaining four cases death was due to irreversible hypoglycæmic coma ; in two cases it occurred in non-diabetic schizophrenic patients. This is, to our knowledge, the first report of the occurrence of selective degeneration of the granular layer in irreversible hypoglycæmic coma. The change was found in three of nine fully investigated cases of hypoglycæmic coma.

The results in our four cases of amaurotic idiocy confirm the finding first established by Bielschowsky (1920), of a frequently selective affection of the granular layer in this condition.

The histological detail of the degeneration of the granular layer requires little comment. In all respects this agrees with previous descriptions and in particular with that given by Bertrand and others (1942), Williams (1934), Winkelman (1943), and Meyer (1944). In all of our three groups of cases the changes range from early conglutination to a complete necrosis of the granule cells. The changes were either focal, as in Case 3 (Fig. 2), in which only a few lobules were affected, or diffuse (Fig. 1), the latter being the more common finding. Even with such a diffuse change, however, there was a not inconsiderable variation in the severity of the lesion from one lobule to the other. In view of these observations it is difficult to draw a sharp dividing line between focal and diffuse varieties of cerebellar atrophy, as was done by Brouwer and Biemond (1938). These authors regard delayed cerebellar atrophy as an example of the former, and the carcinomatous group as an example of the latter. It may be that the cerebellar degeneration occurring with carcinomata, and with other diseases, tends eventually to become diffuse. The same reservation applies to the predilection of the degeneration for the dorsal and medial aspects of the cerebellum, a feature which has been consistently reported in many examples of the delayed Marie-Foix-Alajouanine variety. Bertrand and his associates also observed this selective incidence in the majority of their cases associated with carcinoma and diabetes, but in our material a relative preservation of the ventral parts was seen on only two occasions. Thus, there is no absolute affinity for the dorsal parts of

the cerebellum at least in the carcinomatous and diabetic variety of cerebellar lesion ; it seems more likely that such a transitional distribution tends to occur during the evolution of the process.

Likewise, when we speak of a selective degeneration of the granular layer this does not mean that the lesions were absolutely confined to this part of the cerebellum. In fact, in one of the carcinoma group (Case 5), and one of the amaurotic group (Case 13) the Purkinje cells were slightly reduced in number. There was a more severe loss of Purkinje cells in another of the amaurotic cases (Case 16) and, lastly, in one hypoglycæmic case the Purkinje cells showed very marked acute chromatolysis (Case 10). Evidently, the predilection for the granules is not absolute. This may explain why in some of the carcinoma cases reported in the literature (for example, Zülch, 1936 ; Brouwer and Biemond, 1938) damage was actually more conspicuous in the Purkinje cells than in the granular layer. In the delayed Marie-Foix-Alajouanine group the Purkinje cell affection is usually the main feature, although Garcin and others (1940) reported particularly severe degeneration of the granules.

A striking feature in all our cases associated with carcinoma, hyperglycæmia, and hypoglycæmia, is the absence of an appreciable glial proliferation within the granular layer or other parts of the cerebellar cortex. In some cases there was a moderate gliosis of the white matter. This absence of glial proliferation was also remarked upon by Bertrand and his colleagues. For this reason, and because no cerebellar signs were noted during life, these authors concluded that the cerebellar degeneration occurred in the terminal phase of the disease, for instance, during the terminal cachexia of the patients suffering from carcinoma. It will be remembered that in none of our carcinoma or diabetic-hypoglycæmic cases were clinical signs of disturbed cerebellar function noted. If these cases without glial fibrosis are to be regarded as cases of recent cerebellar degeneration, glial fibrosis should be marked in cases which had exhibited signs of cerebellar dysfunction for some time. There was in fact such a glial fibrosis in all our four amaurotic cases. Unfortunately no reliable clinical data are available to us, but in Norman's (1940) cases of mental defect cerebellar signs had been present for at least the last years of life, and there was very extensive glial sclerosis of all layers of the cerebellar cortex.

At the present juncture it is not possible to offer more than tentative suggestions as to the possible pathogenesis of this type of cerebellar degeneration. It seems that a factor is involved which must be common to such widely different conditions as somatic carcinoma, hyper- and hypoglycæmic coma, and lipoidosis. Courville and Friedman (1940) in discussing the pathogenesis of the delayed (parenchymatous) cerebellar atrophies (in their terminology " chronic progressive degeneration of the superior cerebellar cortex ") suggested that circulatory disturbances produced by arachnoidal thickening were of importance. We have examined the brain of a patient (not included in this series) where, in addition to generalized granular degeneration there was a severe, focal change in the neighbourhood of a subarachnoid hæmorrhage. Quite clearly in this case, circulatory disturbances resulting from the hæmorrhage had played a part in producing a focal granular degeneration. However, it is not clear by what mechanism the focal lesion was produced, and indeed in all the cases reported here there was no evidence of a disorder of the blood vessels. Both vasomotor disturbances and defective utilization of oxygen by the tissues may be of importance ; indeed, it was considered that such mechanisms were intimately concerned in the production of the cerebral lesion found in hypoglycæmic coma (Lawrence and others, 1942). It is possible that hypoxia arises during the terminal phase of the illness in patients suffering from carcinoma. However, in view of the chronicity of the lesion, it is more difficult to postulate that circulatory disturbances or anoxia occurred in amaurotic idiocy. Nor would it be easy to explain why the brunt of the degeneration should have fallen on the granules rather than on the Purkinje cells, which, since Spielmeyer's observations (1922), have so often been shown to be especially susceptible to oxygen want. In a fairly large series of cases of all types of anoxic conditions that have been investigated in this laboratory the granules usually remain intact, whereas the Purkinje cells frequently show the characteristic homogenizing changes. Clearly anoxia alone is not a factor likely to be of ætiological significance.

It might be expected that such a comparatively well-defined metabolic disorder as amaurotic family idiocy would throw some light on the ætiology of the granular layer change. In fact, however, so little is known of the metabolic processes that occur in this condition that it would be speculative to ascribe the granular layer degeneration to any specific factor. However, it may be said that in both our carcinoma group and amaurotic idiocy group, cachexia was a marked feature as in other cases reported in the literature (Lhermitte, 1922 ; Zülch, 1936 ; Norman, 1940 ; Buchanan and others, 1947). Enteritis, alcoholism and cirrhosis hepatis, which might also be expected to lead to profound metabolic disorder, were also prominent

in the cases reported by Murri (1900); Rossi (1907); Lhermitte (1922); Lüthy (1930); Zülch (1936); Norman (1940), and Alessi (1940).

What is known about the biochemistry of this terminal cachexia does not lend itself to even a tentative hypothesis. In Case 1 the combination of granular layer degeneration with the Wernicke's syndrome suggested a thiamine deficiency, as did Upner's experimental findings; but both conditions, clearly, occur more frequently independently than in combination. The relationship of olivary changes to thiamine deficiency appeared, however, to be more consistent. While the inferior olives are known to be very reactive to all kinds of noxious agencies, previous analysis of the literature and personal experience led one of us to assume that olivary damage frequently occurs in conditions associated with metabolic and, in particular, with nutritional disturbances (Meyer, 1944). Particular attention was, therefore, paid to the incidence of olivary changes in the present material, but, again, although the two lesions frequently occur together, they occur too often independently to encourage the assumption of a common specific factor. Pellagra also can be excluded; there was not one case in our histologically verified Pellagra material of about twenty cases which showed degeneration of the granular layer or of the olives.

While there is thus the suggestion that a deficiency factor is concerned in the ætiology of the granular layer degeneration, it is clear that a final solution of the problem must await further investigations.

Summary

Selective degeneration of the granular layer of the cerebellum is described in eight cases of visceral carcinoma, four cases of hypo- or hyperglycæmic coma, and four cases of amaurotic idiocy. The pathogenesis of the lesion is at present obscure, but attention has been directed in this paper to the possibility that some disturbance of metabolism, possibly a nutritional deficiency, is responsible for the degeneration.

It is impossible to make individual acknowledgments to the staff of the various mental hospitals from which we have received the brain material, but we should like to record our special gratitude to Prof. H. A. Magnus of King's College Hospital, who supplied us with the majority of the carcinoma and diabetes cases.

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INTRAMEDULLARY TRIGEMINAL TRACTOTOMY AND ITS PLACE IN THE TREATMENT OF FACIAL PAIN

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When Sjöqvist, in 1938, introduced his operation of dividing the descending tract of the trigeminal nerve within the medulla, interest was aroused in the possibilities of an operative procedure that would abolish pain and temperature sensibility in the face, but would spare touch. During the next few years several surgeons (Rowbotham, 1938, 1939 ; Jackson and Ironside, 1939 ; Smyth, 1939 ; Walker, 1939 ; Grant and various associates, 1940 to 1943 ; Olivecrona, 1942 ; and others) attempted the new procedure, and confirmed that it produces a dissociated sensory loss. Most of these authors, however, pointed out, as did Sjöqvist himself, that the operation was difficult, and was apt to be followed by complications such as paralysis of the vocal cords, ataxia of the ipsilateral arm and of the gait, and impairment of postural sensibility in the ipsilateral limbs. Furthermore, the loss of pain sensation was often only partial and patchy, and indeed sometimes, as in two of Sjöqvist's original nine cases, no sensory loss could be discerned after operation, presumably because the incision had not been correctly placed. The operation was regarded by all as still in the experimental stage.

In an attempt to overcome these difficulties, Grant (Grant and Weinberger, 1941 a, b) and also Olivecrona (1942), the only surgeons besides Sjöqvist to record experiences of more than two or three cases, placed the incision at lower levels in the medulla than Sjöqvist had advised. Olivecrona also advised operating under local anæsthesia so that the level and extent of the incision could be controlled by testing the patient's facial sensibility after each cut. Grant (1943), however, did not consider this practicable " since medullary section is painful, and a sudden movement of the patient at the time of section might result in disaster." Both surgeons hoped that further experience might justify their separate recommendations. However, in nine out of Olivecrona's original thirty cases of unilateral trigeminal neuralgia, the intensity of pain loss resulting from operation was negligible or only slight, while in several of these there was severe pain subsequently. Grant's (1948) experience was even more disappointing, for recently he reported that pain had occurred in five out of six patients submitted to trigeminal tractotomy for major trigeminal neuralgia, and that sensory root section of the trigeminal nerve had proved necessary for permanent relief. He has consequently lost his former enthusiasm for this procedure (Grant, 1948).

Thus most surgeons who have tried trigeminal tractotomy have been somewhat disappointed with their results. My own experience has been more gratifying, for I have now performed this procedure in twenty patients suffering from facial pain of various types, and have observed marked benefit in thirteen patients suffering from trigeminal neuralgia (tic douloureux). Technically it has proved possible in every case to produce a satisfactory level of facial analgesia, sparing touch, and with a minimum of complicating neurological sequelæ. Furthermore, my cases have now all been followed up for a sufficient period (four months to four and a half years) to show that this analgesia and the consequent relief of symptoms is generally permanent.

This paper seeks to review the anatomical and physiological basis of the operation, and to stress what appear to be the points essential to success : (1) the performance of operation under local anæsthesia ; (2) the accurate location of the descending trigeminal tract ; and (3) the correct placing of the incision, which should be below that practised by Sjöqvist and more in accordance with that recommended by Grant and Weinberger (1941 a, b).

Surgical Anatomy and Physiology of the Descending Trigeminal Tract

In order to understand the principles of the operation certain facts concerning the anatomy and physiology of the trigeminal tract must be borne in mind.

Topographical Anatomy.—The trigeminal nerve on entering the ventral surface of the pons penetrates 4 or 5 mm. through the middle cerebellar peduncle (brachium pontis), and then in the lateral portion of the tegmentum it breaks up into ascending and descending fibres. The latter form the descending tract (Fig. 1). As the

FIG. 1.—Prepared specimen of brain stem taken from Grant and Weinberger (1941 b) shows course of descending trigeminal tract (in stipple). The lower half of the right cerebellar hemisphere has been removed to show the fourth ventricle with its lower angle or obex (marked by a small circle). The sites of two incisions are shown : the upper (1) is at the level recommended by Sjöqvist ; the lower (2) at that recommended by Grant and Weinberger. The situation of Olivecrona's incision (not shown) lies midway between these two.

descending tract proceeds downwards it becomes more and more superficially placed, and at the level of the middle of the olive (that is, 8 to 10 mm. cephalic to the lower end of the fourth ventricle), it is covered dorsally and laterally by only the restiform body (Fig. 2a). This is the level at which Sjöqvist (1938 a, b) sectioned the tract, but inevitably section at this level must damage part of the restiform body. Further down its course, just below the fourth ventricle, the tract emerges on the dorso-lateral surface of the medulla, where it forms a well-defined eminence known as the tuberculum cinereum or rolandic tubercle.

At the level of the obex or lower angle of the fourth ventricle (Fig. 2b) the descending tract has not quite emerged from under cover of the fibres of the dorsal spino-cerebellar tract, which however at this situation are running almost at right angles to the longitudinal axis of the brain stem to enter the lower part of the restiform body (Sabin, 1901). This is the level at which

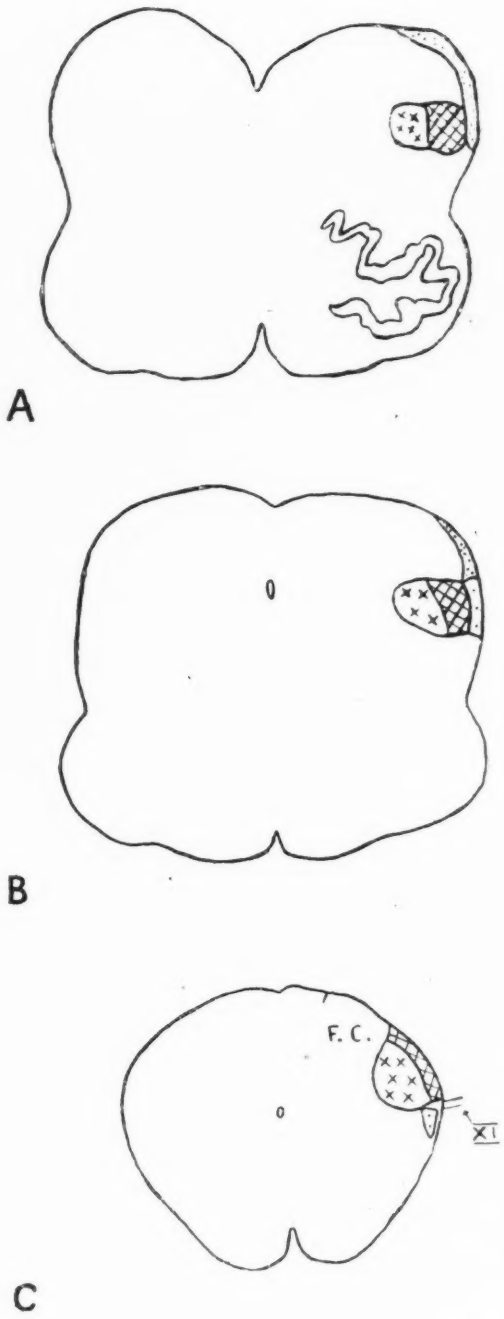

FIG. 2.—Cross-sections of medulla (×4) show relative positions of descending trigeminal tract (cross-hatching), its nucleus (crosses), restiform body (close dots), and dorsal spinocerebellar tract (sparse dots) ; (*a*) shows the relationships at the level of the middle of the olive, (*b*) at the level of the obex, and (*c*) at a level 4 mm. below the obex.

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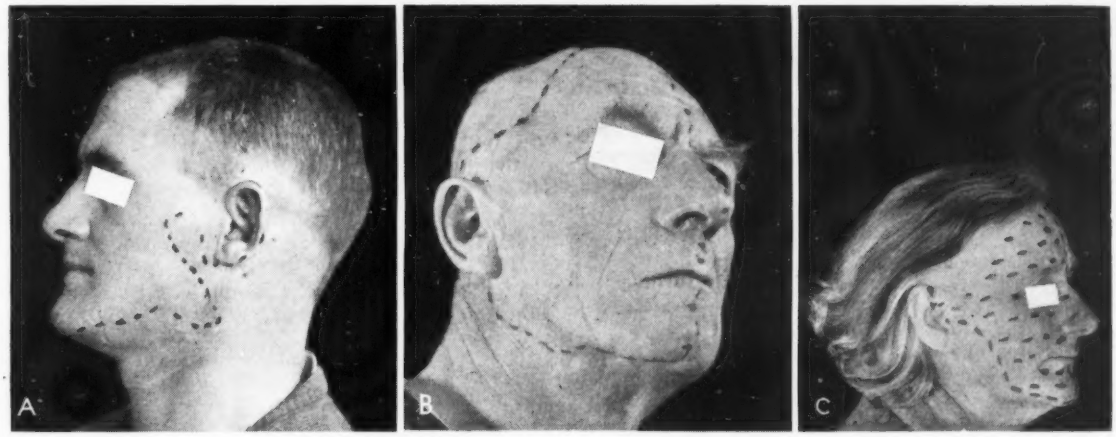

FIG. 3.—Postoperative photographs of three patients showing variations in loss of pain sensibility: (*a*) Case 3, (*b*) Case 5, and (*c*) Case 13.

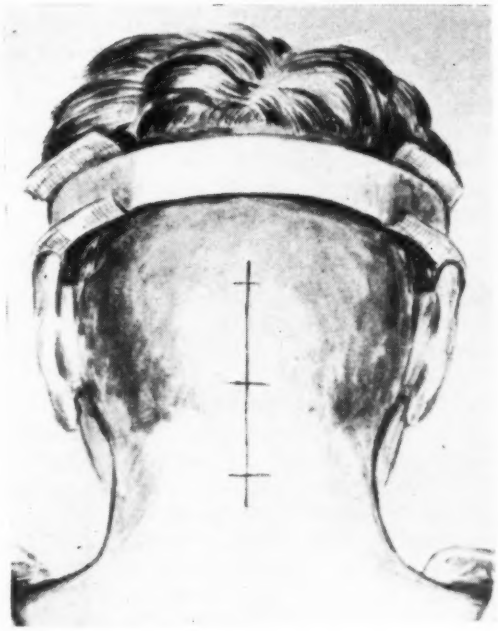

FIG. 4.—Line of incision (From Olivecrona, 1942)

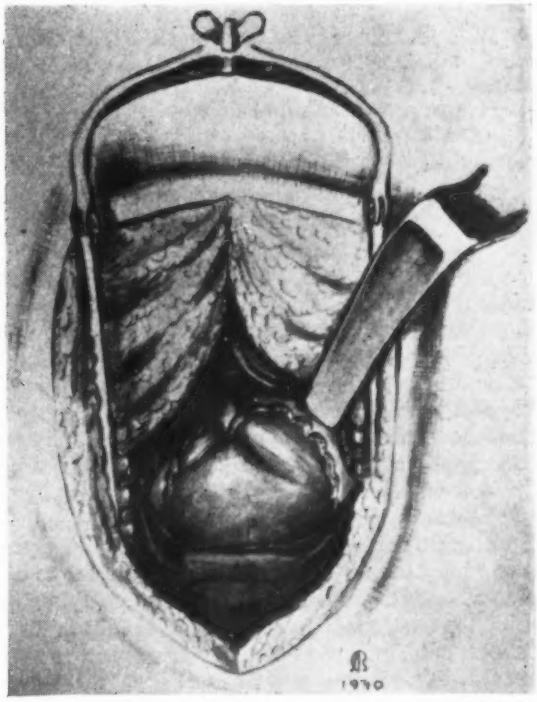

FIG. 5.—Size and form of bone defect in a case of right-sided tractotomy (From Olivecrona, 1942).

Olivecrona (1942) recommended section, and section of the descending tract here may avoid the restiform body, and also spare many of the fibres of the dorsal spino-cerebellar tract, because these are running parallel to the incision.

At a level 4 to 5 mm. below the obex the descending tract occupies the dorso-lateral border of the medulla and is covered only by a few sparse external arcuate fibres (Fig. 2c). This level is that recommended for section by Grant and Weinberger (1941 a, b), and corresponds approximately to the centre of the tuberculum cinereum. At this level the descending tract has wound slightly backwards so that it occupies the dorso-lateral border of the medulla. Medially to it lies the fasciculus cuneatus, while at its anterior margin is the fissure through which emerge the bulbar rootlets of the spinal accessory nerve. The dorsal situation of the descending tract at this level facilitates the operative approach, for the tract can be readily transfixed by a guarded knife inserted from behind in a postero-anterior direction, and not obliquely as is necessary at higher levels.

Below the tuberculum cinereum the descending tract sinks into the substance of the spinal cord and becomes continuous with the marginal fasciculus of Lissauer.

Nucleus of the Descending Root.—Throughout its course the nucleus of the sensory root lies on the medial and deep aspect of the tract. It must be clearly understood that the fibres in the descending tract belong to the primary order of sensory neurones, for they are the axones of cells in the Gasserian ganglion (and also to a slight extent from the sensory ganglia of the seventh, ninth, and tenth cranial nerves). The cells in the nucleus of the sensory tract, however, belong to the secondary order of sensory neurones.

The nucleus of the sensory root is continuous with the substantia gelatinosa of Rolando of the spinal cord.

Types, Arrangement, and Function of Fibres in the Sensory Tract.—It would seem that the descending tract subserves pain and temperature sensibility not only from the fifth, but also from the seventh, ninth, and tenth cranial nerves. Also it would seem that there is a lamination of fibres within the descending tract, so that fibres from the ophthalmic division lie in the ventro-lateral part of the tract, those from the maxillary division in the intermediate part of the tract, and those from the mandibular division in the dorso-medial part of the tract. Further, it would seem that the fibres belonging to the mandibular division are the first to leave the tract, and that they start to do so at or just below the level of the obex ; they are followed by fibres from the maxillary division, whereas fibres from the ophthalmic division continue lowest in the tract towards the spinal cord. Some of the evidence for these various conclusions will be considered.

Sjöqvist (1938) carried out a " fibre analysis " of the sensory root, and showed that it is composed almost exclusively of fibres less than 5 μ in diameter. Fibres of such small dimensions had been shown earlier by Zotterman and others to be responsible for conveying pain and temperature impulses, whereas fibres conveying muscle sense, touch, and pressure sense are all of larger calibre. Sjöqvist, therefore, argued that the descending tract must mediate pain and temperature sensibility, a conclusion which had already been deduced from observations on the clinical effects of posterior inferior cerebellar artery thrombosis (Wallenberg's syndrome), and which since has been established by the abolition of these sensory modalities observed after successful section of the tract.

Sjöqvist also showed that the cross-sectional area of the descending tract remains fairly uniform until the lower pole of the olive is reached (this is just below the level of the obex), but that below this level it decreases rapidly in size. That the first fibres to leave the tract do so on its dorso-medial border and come from the mandibular division has been suggested by many authorities, and also by my own observations on the effects of systematically sectioning the tract at varying levels in patients under local anæsthesia. Thus I have found that, whereas at a level of 4 mm. or so below the obex one can readily denervate the upper two divisions of the face, the lower division may be difficult to denervate at this level. Instead, in order to denervate the third division, the incision has often to be made at or slightly below the level of the obex, and has to be carried into the dorso-medial part of the tract. I would however qualify this statement by adding that sometimes an incision as low as 4 mm. below the obex has produced satisfactory analgesia in all parts of the face. Weinberger and Grant (1943) have also observed this.

Brodal (1947) first drew attention to the full extent of the analgesia that follows section of the descending tract. Sjöqvist in his original communication reported that the area of analgesia often extended below the angle of the jaw into the territory of the cervical plexus, but Brodal showed also that a dissociated analgesia is frequently produced in the region of the concha of the external ear (territory of the cutaneous branches of the seventh and tenth cranial nerves) and in the region of the posterior third of the tongue, the tonsillar fossa, and the pharynx (territory of the ninth cranial nerve). My own observations substantiate those of Brodal (Fig. 3a, b, c). From the phylogenetic point of view this is in accordance with the tendency noted elsewhere in the central nervous system for fibres conveying the same type of impulse to pass to the same nucleus.

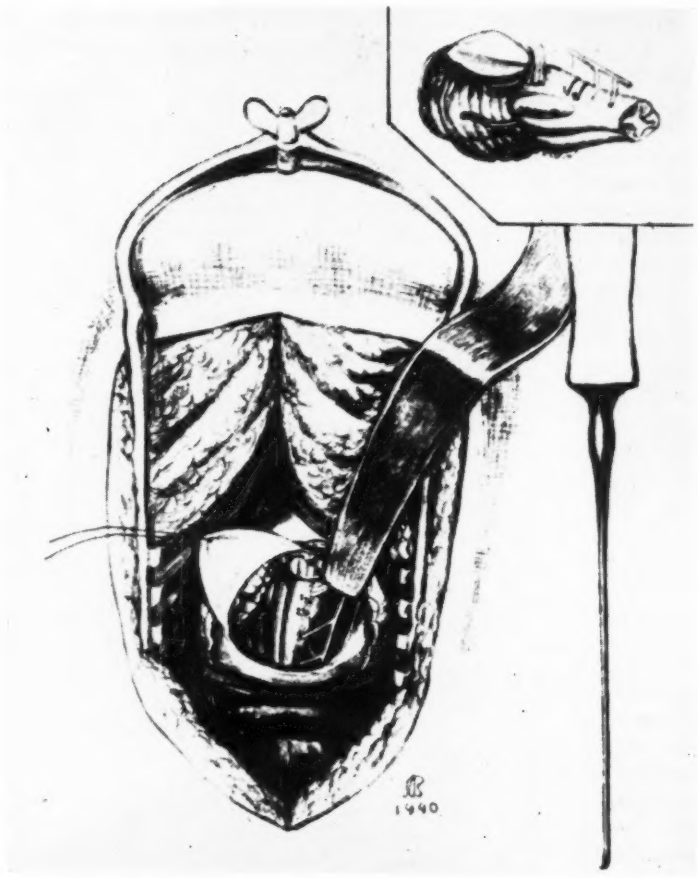

FIG. 6.—Level of incision into the medulla: (1) indicates site of Sjöqvist's original incision, (2) site of Olivecrona's incision. Recommended site is 4 mm. below (2). (From Olivecrona, 1942).

Technique of Operation

In all except two of my first twenty cases the operative approach up to and including the section of the medulla was performed under local anæsthesia employing 1 per cent. procaine solution. Preliminary medication has usually been with morphine sulphate gr. 1/6 and hyoscine hydrobromide gr. 1/100 or 1/150 given hypodermically.

Each patient has been operated on in the prone position, and the surgical exposure outlined by Olivecrona (1942) has been followed. In Olivecrona's words the steps of this exposure are as follows.

"A straight incision is made from a point just below the occipital protuberance to the spinous process of the third cervical vertebra (Fig. 4). The soft parts are divided exactly in the midline. The insertions of the short rotators of the head are freed from the occipital bone and their origin on the atlas is divided with the diathermy needle. After a sufficient area of bone has been exposed two burr holes are made. The subsequent nibbling away of bone is much facilitated if two burr holes, instead of the customary single one, are made. Bone is then rongeured away until a sufficient area of dura is exposed (Fig. 5). The posterior rim of the foramen magnum is of course removed. The dura is then opened by a V-shaped incision (Fig. 6). The occipital sinus may occasionally be large, but hæmorrhage from this source can always be controlled by silver clips. After incising the arachnoid and evacuating the fluid in the posterior cistern, the tonsil on the side of operation is gently elevated and a suitable point for incision into the spinal trigeminal tract selected."

Selection of Site for Incision.—Like Olivecrona, the principal landmark we seek is the obex or lower end of the fourth ventricle. Usually this is readily found, and at the same time a good view of the foramen of Magendie is obtained. Occasionally, however, a loop of a posterior inferior cerebellar artery runs across this particular part of the field and may have to be displaced before the obex is clearly seen. In one case, attempted after my first twenty cases, the lower end of the fourth ventricle was occluded by a stout imperforate septum without trace of a foramen of Magendie, and the operation had to be abandoned because a suitable landmark could not be found. This, however, has happened only once in twenty-four operations.

The second landmark is the line of emergence of the bulbar rootlets of the spinal accessory nerve on the lateral aspect of the medulla. This marks the line of the ventrolateral border of the descending tract. The rootlets are not contiguous, like the rootlets of the vagus nerve, but are separated from one another. Sometimes they are hidden by the vertebral artery as it runs vertically upwards lateral to the medulla, and then the landmark may be only approximately placed.

Once the obex has been identified, the locating of the descending tract is not difficult. Sometimes the tuberculum cinereum can be discerned as an eminence lying below and lateral to the obex along

the dorso-lateral border of the medulla, but more often no definite eminence is discernible. In this event some tiny vascular marking is noted on the dorsal surface of the medulla at a level approximately 4 mm. below the obex, and then, with this marking as a guide to the transverse level of the incision, the posterior surface of the medulla lateral to the midline is divided into equal lateral and medial portions. The lateral portion thus located, including the dorso-lateral border of the medulla, usually corresponds with the course of the descending tract.

Verification of Correct Site for Incision.—Until recently I used to incise the medulla at the site so marked, and could afterwards tell from the result how accurate was my trial incision and whether it required extending. Now I use a straight surgical needle mounted on a long handle, and I first prick the medulla to depths of about 3 mm. along the line of the proposed incision in order to verify the position of the descending tract. For, as the descending tract is pierced, slight momentary pain is felt in the appropriate part of the face. In this way the situation of the descending tract can be mapped out accurately before the incision is made.

The actual incising of the tract is done with a straight tenotomy knife. This is inserted transversely to a depth of 3 mm. along the dorso-medial border of the tract, and is then directed outwards so as to emerge on the surface of the medulla along the ventro-lateral border of the tract (here marked by the line of the bulbar rootlets of the spinal accessory nerve). The incision if correctly placed is very painful, although not quite as painful as section of a posterior nerve root. The pain, however, is momentary, and it is itself a guide to a satisfactory incision, for unless pain is severe a satisfactory loss of pain sensibility cannot be expected. Some of our patients have screamed at this stage ; but, probably because we have always warned them beforehand, none has shifted his position on the operating table. As soon as the momentary pain is over, the anæsthetist checks pain sensibility in the face, and reports on the extent and degree of analgesia. If this is patchy, the incision is extended. Owing to the toughness of the arachnoid it is impossible to complete the incision in one stroke. Therefore two and even three strokes are normally required to complete the incision, and for one of these secondary cuts I have usually employed a 3 mm. fragment of safety-razor blade set at right angles in the tip of an artery forceps (Fig. 7). This I have inserted at the ventro-lateral border of the tract, and then cut backwards.

As my experience has grown, I have become accustomed to placing the incision accurately at the first trial, and to securing prompt analgesia over the side of the face. In some of my earlier cases I was not so fortunate, and it was from these cases that I learnt about the lamination of fibres within the descending root. It is easier in this operation to denervate the upper two divisions than the lower division, and an incision into the dorso-

FIG. 7.—Fragment of razor-blade set in tip of artery forceps used in making the incision.

lateral border of the medulla at a level 4 mm. below the obex will generally produce analgesia over the forehead and cheek, and often over the third division as well. If by any chance the ophthalmic division is spared by the first stroke, the incision should be extended in a ventro-lateral direction. If, however, the mandibular division is spared and analgesia of this division is required, the original incision may be extended with great caution dorsally to the mid-point between the dorso-lateral border of the medulla and the midline, but generally it is prefer-

able to make a fresh incision at a higher level (say opposite the obex). In no circumstances, if an incision is a failure, should it be deepened to more than 3 mm., but instead a new incision should be made either higher or lower, and it is astonishing how often at a new level only 2 or 3 mm. away a satisfactory result may be forthcoming.

Usually the incision into the medulla is bloodless, but sometimes bleeding occurs and necessitates the application of a muscle pledglet. If a tiny arterial twig crosses the line of the proposed incision, I do not hesitate to coagulate it with a diathermy current applied through a slender hook before making the incision.

Closure.—Once a satisfactory degree of analgesia has been obtained our patients have usually been given an intravenous pentothal anæsthesia and the closure has been made under this. The incision in the dura is sutured as neatly as possible, and the occipital muscles closed in layers.

Postoperative Course.—Our usual programme has been to keep the patient in bed for ten days before allowing him up. Generally daily lumbar punctures are performed, and 10 to 20 ml. of cerebrospinal fluid are drained off until the lumbar puncture pressure returns to normal and there are less than 50 white cells per c.mm. in the cerebrospinal fluid. This usually takes a week, and in this way we believe we guard against the development of an aseptic leptomeningitis (Finlayson and Penfield, 1941). Our patients have usually left hospital within sixteen to twenty days, and returned to work within two to three months.

Comments on the Operative Procedure

The operative steps described above are identical with those described by Olivecrona (1942), except as regards the placing of the incision and the method of determining the precise situation of the tract by needling before sectioning it. The essential points in the operation are :

1. Performance under Local Anæsthesia.—Olivecrona (1942) seems to have been the only surgeon to recommend local anæsthesia for this procedure. Sjöqvist (1938) and those who have followed his technique, including Grant and his various associates (1940 to 1943), have all performed trigeminal tractotomy under general anæsthesia in order to avoid the pain inseparable from section of the tract. Even under light inhalational anæsthesia Sjöqvist has noted that patients may wince when the tract is being cut. It is of course impossible in such circumstances to define the position of the descending tract by pricking the medulla, and, more important still, to test the patient's facial sensibility after each cut. The chances of an unsatisfactory technical result are therefore increased.

My experience has been that the operation usually can be performed under local anæsthesia. I was able to do so satisfactorily in eighteen of my twenty cases. In one case (Case 20) in which operation was begun under local anæsthesia, an intravenous anæsthetic became necessary at an early stage because of the patient's restlessness and anguish ; and in this case a second craniotomy (also under general anæsthesia) proved necessary a few days later because the incisions made at the first operation had severed only part of the tract. In the other case (Case 18) operated on under general anæsthesia, the patient previously had had more than ten operations for lupous ulcers of the face performed by plastic surgeons, all under general anæsthesia, and she obviously would not have tolerated local anæsthesia alone.

2. Midline Occipital Craniotomy.—This is simpler and easier to perform than the unilateral cerebellar exposure employing a curved incision used by Sjöqvist (1938) and those who have followed his lead. At the level in the medulla which Sjöqvist favoured, it was necessary when incising the tract to approach the medulla on its lateral aspect, and the removal of bone laterally over the appropriate cerebellar hemisphere facilitates this. However, when the incision is made at levels below the obex, the point of the knife can be inserted into the medulla directly from behind, and there is no need for a wide craniotomy.

It is unnecessary to remove the arch of the atlas vertebra in either the Sjöqvist or the Olivecrona approach.

3. Locating the Descending Tract.—It is easier to locate the position of the descending tract at or below the level of the obex than at a higher level, for less retraction of the cerebellar tonsil is required. Moreover, with the lower cut the vagus rootlets and the olivary eminence need not be exposed.

The method of confirming the location of the descending tract by pricking the medulla has so far been tried by me in only a few cases, but it has proved helpful.

4. Level of Section of Tract.—At a level 4 mm. or so below the obex it is possible to produce a satisfactory degree of analgesia in most cases, particularly in the first and second trigeminal divisions, and sometimes also in the third division. Furthermore, because the tract is superficial at this level, the risk of damage to neighbouring structures such as the restiform body is minimized, and injury to

the vagus nerve, a risk ever present in the Sjöqvist procedure, is completely avoided.

5. Testing Analgesia after each Cut in the Medulla.—This of course has to be done by some doctor outside the operating team. The incision is considered satisfactorily placed only when the patient can no longer discriminate between the blunt and the sharp end of a pin over that part of the face where pain was complained of spontaneously. In most instances this has been the first division (*vide infra*).

6. Subsequent Incision if First is Unsatisfactory.—If, at operation, complete analgesia is not forthcoming after an incision which seems to be correctly placed, a second incision should be made at another level, as mentioned in the preceding section. Again if, a few days after operation, sensory testing shows that pain loss, which seemed complete while the patient was on the operating table, has disappeared or become patchy, the operative area should be reopened. Then, depending on the pattern of sensory change, the original incision should be extended or another made at a different level. In my series of twenty cases reopening of the craniotomy had to be undertaken in three.

7. Operative Risks.—Trigeminal tractotomy carries the same risks as a suboccipital craniotomy for such elective procedures as intracranial section of the eighth or ninth cranial nerves. In skilled hands the operative mortality should be low. In my series of twenty cases there was one death from extradural clot compression, and in this patient symptoms came on suddenly on the fifth postoperative day. Post-mortem examination indicated that death in this case could have been prevented, had the nature of the complication been recognized in time and the operative area reopened. The relevant points of the history follow :

Case 4 : *Death on Fifth Postoperative Day from Extradural Clot Compression.*—In a 57-year-old woman suffering from post-herpetic neuralgia of the upper trigeminal division, trigeminal tractotomy was carried out without undue difficulty. For the first five days after operation she seemed to be progressing satisfactorily. She was free from her pain and had little headache. Lumbar punctures repeated daily showed pressures of under 200 mm., and the cerebrospinal fluid, which had been moderately bloodstained, seemed by the fifth day to be clearing.

She was placed in a room by herself, and after she had eaten a good lunch on the fifth postoperative day she told the nurse she felt all right, and so was left alone for a post-prandial nap. When seen an hour later she appeared to be sleeping, and so was not disturbed. Two hours later, however, her respirations were found to be slow and laboured, and she could not be roused. Her lower limbs would move in response to painful stimuli but not her upper limbs. The tendon jerks were depressed. The pupils were small and equal, and plantar responses both extensor. Lumbar puncture showed a fairly clear cerebrospinal fluid under a pressure of only 20 mm. Blood pressure was unaltered at about 170/80 mm. Hg. It was thought she must have had an " apoplectic stroke."

She died about three hours later, developing pyrexia in the terminal stages. At necropsy a large extradural clot was found beneath the muscles and indenting the dura of the posterior fossa. It was firm and friable, and was considered by the pathologist (the late Dr. John Sutherland) to have been present for several days. It was unfortunate that the nature of her coma had not been interpreted correctly, for re-exploration with removal of this clot would probably have saved her life. We were misled by the fact that before the sudden loss of consciousness she had appeared to be progressing well and had not complained of any untoward symptoms. Yet the post-mortem examination showed that the clot had probably been there from the time of her operation.

Case-Material and Results of Operation

Between August 1944 and March 1949, intramedullary trigeminal tractotomy has been performed by me in twenty patients, including one who in two separate sessions had the operation performed on both sides for bilateral trigeminal neuralgia. These patients included examples of the following different conditions : (*a*) unilateral trigeminal neuralgia (eleven patients, all relieved) ; (*b*) bilateral trigeminal neuralgia (two patients, both relieved) ; (*c*) " syndrome of painful anæsthesia " following complete section of the sensory root of the trigeminal nerve performed for trigeminal neuralgia (two patients, both improved) ; (*d*) postherpetic neuralgia affecting the face (four patients : one died, and none benefited) ; (*e*) causalgia of face secondary to lupus (one patient, not benefited).

Twelve of these twenty patients were males and eight were females. Their ages varied from 34 to 70 years, with two patients in the fourth decade of life, three in the fifth, seven in the sixth, five in the seventh, and three over seventy years of age. There was one death occurring in hospital (mortality rate 5 per cent.). Two patients have since died of unrelated causes, and the surviving patients have been followed up for periods up to four and a half years. All patients except one have been examined personally by me at some stage after their discharge from hospital, but in most instances the more recent follow-up enquiries have been carried out by letter to the patient or his doctor. The clinical features of each patient are summarized in the Table.

The results achieved will be studied, firstly as regards the physiological effects of the operation, and secondly as regards its therapeutic benefits.

Physiological Effects of Operation

In all cases (excluding of course the first two cases in the series, because, as the result of a previous sensory root section, they already exhibited complete cutaneous sensory loss) a satisfactory loss of pain sensibility was produced in the face, usually with complete sparing of touch but with loss of temperature sensibility. Moreover in all instances this loss of pain sensibility appears to have been permanent. Generally the degree of pain loss was complete even to heavy pin prick over all three divisions of the trigeminal nerve. In four cases (Cases 5, 7, 13, 16), however, it was complete in the upper part of the face but incomplete in the third division.

In most cases the area of pain and temperature loss extended beyond the territory of the trigeminal nerve. For instance, analgesia was often noted around the angle of the jaw which is in the territory of the cervical plexus. With one exception, whenever sensation was deliberately tested in the region of the concha of the ear (seventh and tenth cranial nerves), and of the tonsillar fossa, pharynx, and soft palate (ninth cranial nerve), analgesia with sparing of touch was noted in these areas. Unfortunately not until I had read Brodal's (1947) paper was I made aware that these areas are commonly involved, and several patients consequently have not been examined in this respect.

In most cases the sensation of touch as tested with a cotton-wool wisp, appeared to have been completely spared. As after chordotomy, however, the sensation of touch becomes bereft of any concomitant feeling of tickle, and some patients will notice the difference. In a few patients, however, a slight but definite impairment of tactile sensibility appeared to be present. Weinberger and Grant (1942) considered that touch was frequently impaired, but Sjöqvist (1938) and Smyth (1939) did not find this.

In all cases pain sensitivity was lost in the cornea, although a feeling of touch remained. The corneal reflex was usually greatly diminished and sometimes seemed almost absent. In no instance did any signs of neuropathic keratitis develop subsequently, nor were any special precautions taken to avoid this complication.

In six cases slight but permanent ataxia has persisted after operation, but this is the only undesirable neurological complication noted in this series, and in no instance has it been disturbing. Several patients exhibited ataxia in the immediate postoperative stage, but this soon disappeared. No case developed laryngeal palsy nor any loss of postural sensibility in either arm or leg. There was no instance of masticatory paralysis.

The only other complication seen in this series was a herpetic eruption, usually in the upper or lower lip, but sometimes in the forehead. This occurred in about half the cases and appeared between the second and sixth postoperative days. In every respect the eruption was similar to that so commonly seen after section of the sensory root of the Gasserian ganglion, and likewise proved temporary.

The physiological effects of intramedullary tractotomy were thus uniformly gratifying in my series. There was no case in which a satisfactory loss of pain sensibility was not produced in the face. In this respect, therefore, the results achieved in this series of cases are superior to those recorded by previous authors, but before these results were attained a second or even third incision at a slightly different level had to be made in the medulla in thirteen cases; in three cases a second operation proved necessary to complete the incisions.

Therapeutic Effects of the Operation

In Trigeminal Neuralgia.—Observations in this series confirm previous reports that benefit from this operation is principally in the field of trigeminal neuralgia. Permanent benefit was seen in eleven cases of unilateral trigeminal neuralgia, and in two cases of bilateral trigeminal neuralgia. Many of my patients were elderly and retired, but all those who were operated upon while still in the period of their active working life have since returned to their normal occupations.

With one exception all the patients with unilateral trigeminal neuralgia suffered from pain in the first or second divisions of the nerve. The exception (Case 14) was a man with third-division as well as second-division pain, who already had a complete and permanent facial palsy and consequently ran an almost certain risk of neuropathic keratitis if his cornea were completely denervated. The operation proved successful and, although the cornea was rendered analgesic, touch was present in it and he has not had trouble with his eye. In another case (Case 5) with exceptionally violent trigeminal neuralgia, the pain had originated in the third division, but during the particular attack which caused his referral for operative treatment the pain spread over the side of his face. The tractotomy relieved pain in the first two divisions, but a partial sensory root section was subsequently required to ease the pain in the third division.

All patients with unilateral trigeminal neuralgia when followed up expressed themselves as very

TABLE.—PARTICULARS OF CASES TREATED BY

A. CASES OF PERSISTENT PAIN FOLLOWING COMPLETE SECTION OF SENSORY

Chronological case no.	Sex; age in years; referring doctor	Clinical features			Previous operations	Particulars of tractotomy		
		Duration (yrs.)	Intensity of pain	Division affected		Level of tractotomy above or below obex	No. of operative sessions needed	Complications
1	F. 44 Drs. R. H. Q. Baxter and C. H. Thomson	6	Severe: aching	I, II	Complete sensory root section 5 yrs. before complicated by neuropathic keratitis resulting in loss of eyeball	At level of obex	1	—
2	F. 57 Drs. R. H. Q. Baxter and M. Robertson	16	Severe: burning	I, II, III	Complete sensory root section 6 yrs. before complicated by neuropathic keratitis and loss of eyeball	At level of obex	1	—
	B. CASES OF POST-HERPETIC							
4	F. 57 Dr. G. Barnett	15	Severe	I, II	Avulsion of supraorbital, supratrochlear, and infraorbital nerves 6 mths. before	At level of obex	1	Died on 5th post-operative day of clot compression
7	F. 56 Drs. R. H. Q. Baxter and A. H. Stewart	5	Severe	II	Intracranial section of II division 2½ yrs. before	Two cuts, at level of obex and 3 mm. below	2	—
9	F. 58 Drs. J. Willis and D. Y. Allen	3	Severe		—	At level of obex	1	—
10	M. 70 Drs. R. Bevan-Brown and R. S. Fitzgerald	1	Severe	III	Partial sensory root section 6 mths. before	Three cuts, 2 mm. above, at level of obex, and 3 mm. below	1	—
	C. CASES OF UNILATERAL							
3	M. 35 Dr. D. M. Logan	3	Moderate	I	Alcohol infiltration of supraorbital and supratrochlear nerves 2 yrs. before	Two cuts: at level of obex, and 3 mm. below	1	—
5	M. 63 Dr. D. S. Wyllie	4½	Very severe	I, II, III	Several alcohol injections of trigeminal nerve branches	Two cuts: at level of obex, and 3 mm. below	1	—
6	F. 60 Dr. I. M. Allen	5	Severe	II	Intracranial section of II division 2 yrs. before. Regenerated	Two cuts: at level of obex, and 3 mm. below	2	—
8	M. 34 War pensions	4	Severe	I	Partial sensory root section for II division neuralgia 1 yr. before	At level of obex	1	—
11	F. 60 Dr. R. Burns Watson	3	Severe	I	Avulsion of supraorbital and supratrochlear nerves 6 mths. before. Regenerated	Two cuts: at level of obex, and 3 mm. below	1	—
12	M. 40 Dr. H. Hunter	2	Severe	I, II	Alcohol infiltration of supraorbital and supratrochlear nerves	Two cuts: 2 mm. and 4 mm. below	1	—
13	F. 59 Drs. R. H. Q. Baxter and H. W. Duncan	⅛	Severe	I	—	Two cuts: at level of obex, and 4 mm. below	1	—
14	M. 68 Dr. R. S. Fitzgerald	5	Severe	II, III	40 yrs. previously excision of half mandible for osteomyelitis. Operation followed by facial palsy	Two cuts: at level of obex, and 4 mm. below	1	—
16	F. 68 Dr. J. E. Caughey	16	Severe	I, II	Alcohol injection of infraorbital nerve 3 mths. before	Two cuts: 2 mm. and 4 mm. below	1	—
17	F. 70 Sir Hugh Cairns	13	Severe	II	Partial sensory root section, and avulsion of infraorbital nerve several yrs. before	4 mm. below	1	—
19	M. 48 Dr. A. Wardale	4	Severe	I, II	Alcohol injection of infraorbital nerve 1 yr. before	Two cuts: 3 mm. and 5 mm. below	1	—

INTRAMEDULLARY TRIGEMINAL TRACTOTOMY

ROOT OF TRIGEMINAL NERVE PERFORMED FOR TRIGEMINAL NEURALGIA

Distribution and grade of analgesia after tractotomy					Period of follow-up after tractotomy (yrs.)	Follow-up results				General impression of end-result
Trigeminal nerve division I	II	III	9th cranial nerve	10th cranial nerve		Persistent or recurrent pain	Paræsthesias of face	Other neurological sequelæ	Further operative procedures required	
Complete analgesia already present before tractotomy			?	?	4½	Pain disappeared from forehead, but still present in socket of eye	—	Slight ataxia of ipsilateral upper limb	—	Improved. Recently committed suicide, ? due to other causes
Complete analgesia already present before tractotomy			?	?	4½	Still pain in all three divisions, but less severe than before	—	—	—	Improved
TRIGEMINAL NEURALGIA										
+	+	+	?	?	—	—	—	—	—	Postoperative fatality
+	+	±	+	+	3½	Pain disappeared temporarily, then recurred spreading into III division	—	—	—	Worse
+	+	+	+	+	3	Pain lessened for 6 mths., then recurred	—	—	—	Not improved
+	+	+	+	±	2½	Pain not altered	—	—	2 mths. later prefrontal leucotomy performed	Benefited from leucotomy, but not from tractotomy. (Reported in detail: Falconer, 1947)
TRIGEMINAL NEURALGIA										
+	+	+	+	+	4	No pain	Sometimes tingling over side of nose	Slight ataxia of ipsilateral upper limb	—	Satisfactory
+	+	±	±	±	2	Pain in I and II divisions permanently relieved, but returned in III division 2 mths. later	Tingling sensations in cheek at times	Slight ataxia of ipsilateral upper limb	Partial sensory root section performed 3 mths. later	Benefited by tractotomy. Result good after sensory root section. Died of coronary attack 2 yrs. later
+	+	+	+	+	4	No pain	Very slight aches	—	—	Good
+	already analgesic		±	±	3	No pain	Slight aches	—	—	Good
+	+	+	+	+	2½	No more pain at former site	Painful sensations at times in right ear associated with chronic otitis; relieved by new dentures; infrequent painful flickers over lower face	—	—	Eventually good
+	+	+	?	?	2½	No pain		—	—	Good
+	+	±	+	+	2	Free from old pain	Slight nagging pains in upper face	Slight ataxia of ipsilateral upper limb	—	Satisfactory
+	+	+	+	+	2	No pain	Occasional tingles	Slight ataxia of ipsilateral upper limb	—	Satisfactory
+	+	±	+	+	1½	No pain	Occasional pins and needles	—	—	Good
+	+	+	−	−	—	No pain	Some aching	—	—	Good
+	+	+	+	+	1	No pain	Occasional twinges but not severe	—	—	Good

[*Continued overleaf*

TABLE—

D. CASES OF BILATERAL

Chronological case no.	Sex ; age in years ; referring doctor	Clinical features			Previous operations	Particulars of tractotomy		
		Duration (yrs.)	Intensity of pain	Division affected		Level of tractotomy above or below obex	No. of operative sessions needed	Complications
15	F. 50 Dr. G. Rich	5	Severe	III	Several alcohol injections, and intracranial section of III division 3 yrs. before	Two cuts : 2 mm. and 4 mm. below	1	—
	Readmission 1½ yrs. later	1½	Severe	II on opposite side	Alcohol injection of II division 15 mths. before	3 mm. below	1	—
20	M. 63 Dr. E. McLaglan	12	Severe	II	Alcohol injection of contralateral Gasserian ganglion for tic douloureux on opposite side of face 1 yr. before. Relieved	Three cuts : 2 mm., 4 mm., and 6 mm. below	2	—

E. CASE OF FACIAL CAUSALGIA

18	F. 70 Dr. G. Barnett	20	Severe	I, II	Alcohol injection of supraorbital, supratrochlear, and infraorbital nerves 2 mths. before had aggravated pain	Two cuts : at level of obex, and 4 mm. below	1	—

pleased with the results of operation. Some had had their pain for many years, and most had had other operative procedures performed but pain had recurred. All patients, however, sometimes only after they had been questioned specifically, reported that they still experienced some unpleasant sensations in the analgesic area, particularly in the form of pins-and-needles, tingling pains, or itching sensations. None, however, seemed upset by these persisting paræsthesias. Comparable paræsthesias are seen in a large proportion of patients after a partial sensory root section.

The two cases of bilateral trigeminal neuralgia were also benefited. In one (Case 15) the operation was performed in two sessions spaced one and a half years apart, and this patient was restored to her full life without any ataxia. The other (Case 20), a chronic tabetic, had the operation performed on the second side because he had already undergone an alcohol injection of the Gasserian ganglion which had completely denervated the first side. Since the tractotomy on the second side he has been free from pain and has not experienced those difficulties in eating and talking which characterise bilateral alcohol injections of the Gasserian ganglion.

In two other cases of trigeminal neuralgia, the first two cases in my series, a complete section of the sensory root had been performed several years before and had been followed by persistent and severe pain in the anæsthetic area. Such cases fortunately are not common, but they occur in every neurosurgeon's experience (Olivecrona, 1939 ; Grant, 1938, 1948 ; and others). They are very intractable, and it was the distressing condition of my first patient that led me to try this procedure. Four and a half years later both patients said they were improved, although both continued to complain of pain. At the time of operation it proved difficult, because of the pre-existing facial analgesia, to ascertain whether the descending tracts had been severed or not. The only guide available to us was pain in the face at the moment of the incision, and in the light of my subsequent experiences with this operation I wonder how complete technically the operation in these two cases really was.

In Other Conditions.—I have tried the operation in two other groups of conditions, postherpetic neuralgia and causalgia of the face secondary to a lupous ulcer of the nose for which many plastic procedures had been carried out. No case was benefited, and some indeed were made worse. Three of the four cases of postherpetic neuralgia were temporarily relieved from pain, but in the three surviving cases pain returned as severely as ever. One case has since been benefited by prefrontal leucotomy, and this case has already been reported in detail (Falconer, 1947). He remains benefited nearly three years after this latter procedure. Sjöqvist (1938 b) had reported failure of the operation to relieve pain in one case of postherpetic neuralgia.

I have not yet had the opportunity of trying this operation for the relief of facial pain occasioned by malignant disease. Grant (Grant and Weinberger, 1941 ; Grant, 1943) has reported several successful cases. Also I have not had experience in the treatment of glossopharyngeal pain by this opera-

continued

TRIGEMINAL NEURALGIA

Distribution and grade of analgesia after tractotomy					Period of follow-up after tractotomy (yrs.)	Follow-up results				General impression of end-result
Trigeminal nerve division			9th cranial nerve	10th cranial nerve		Persistent or recurrent pain	Paræsthesias of face	Other neurological sequelæ	Further operative procedures required	
I	II	III								
+	+	+	+	±	2	Pain relieved on that side	Slight tingling	—	—	Good
+	+	+	+	+	½	Pain relieved on second side	Slight tingling	—	—	Good
+	+	+	+	+	½	No pain	Slight aching	Slight increase of ataxia in ipsilateral upper limb	—	Satisfactory result in a tabetic
SECONDARY TO LUPUS VULGARIS										
+	+	+	?	?	1½	Pain disappeared temporarily, then recurred more extensively	—	—	—	Worse

tion. The fact that the operation will produce analgesia in the territory of the glossopharyngeal nerve suggests that, by itself, it might prove effective in painful conditions in the tonsillar fossa, pharynx, and hinder part of the tongue. Probably it would be wiser in painful conditions due to malignant disease affecting the pharynx to combine the procedure with an intracranial section of the glossopharyngeal nerve, as Grant (1943) has advised.

Trigeminal tractotomy has also been tried by Olivecrona (1947) for the treatment of migraine. Eight out of thirteen cases in his series appear to have been benefited. Olivecrona, however, concludes his article by drawing attention to Gardner's (Gardner and others, 1947) procedure for migraine of division of the greater superficial petrosal nerve, and reports two successful cases. In this neurosurgical clinic we have since tried Gardner's procedure in a number of cases, usually with gratifying results. I have therefore not had occasion to try tractotomy for migraine.

Conclusions : Indication for Operation

From personal experience I would say that there are three main indications for intramedullary trigeminal tractotomy. They are : (1) cases of first and also possibly second division trigeminal neuralgia (tic douloureux) ; (2) cases of bilateral trigeminal neuralgia (tic douloureux) ; (3) cases of persistent pain following complete sensory root section performed for trigeminal neuralgia.

To these indications can probably be added a fourth : intractable facial pain secondary to malignant disease. As I have not had experience of it I shall not discuss this indication further.

First and Second Division Trigeminal Neuralgia.—For cases of trigeminal neuralgia involving the third or second divisions of the nerve (which comprise most cases of tic douloureux) the operation of partial section of the sensory root of the Gasserian ganglion, sufficient fibres being left in the inner part of the root to preserve sensation in the forehead and cornea, is a satisfactory procedure. Moreover it is well standardized and carries little risk to life. It is likely to remain the routine procedure for these cases.

The therapeutic problem, however, is altered when first-division neuralgia is considered, for if sensory root section is employed in these cases the cornea is inevitably denervated at the same time as the forehead, while if lesser procedures are used, such as avulsion of the supraorbital and supratrochlear nerves, the chances of persistent or recurrent symptoms are considerable. An insensitive cornea is to be avoided, as it is apt to be followed by neuropathic keratitis, especially when a temporary facial palsy is also present, as not uncommonly occurs after sensory root section.

More and more I am coming to the view that for first-division trigeminal neuralgia, trigeminal tractotomy is the procedure of election. The same conclusion probably also holds true for those cases of second division neuralgia where the pain is located close to the eyeball or secondarily spreads to the first division, for it is usually impossible to relieve these cases of their periorbital and forehead

pain by graduated sensory root section without denervating the cornea (see Cases 8 and 15 in the Table). Fortunately the first two divisions are the ones most readily denervated by the intramedullary operation, and they can usually be rendered analgesic without the appearance of permanent ataxia from interference with the restiform body. As touch is preserved in the cornea, there is no risk of neuropathic keratitis, nor is there any risk of facial palsy.

Bilateral Trigeminal Neuralgia.—Fortunately this is not common, but hitherto when it has occurred it has been a very difficult therapeutic problem. A patient with complete loss of sensation over the lower part of his face on both sides is to be pitied, for he loses postural sensibility in his lower jaw and can eat only when he looks at his mouth in a mirror or touches his jaw with his hand. The lot of the patient who has also an associated bilateral masticatory weakness is miserable in the extreme, for he can only eat when he holds and moves his lower jaw with his hand.

Fortunately both these distressing states are avoided by trigeminal tractotomy, for after this operation touch is preserved and there is no disturbance of postural sensibility in the jaw, nor any risk of a masticatory paralysis. Of course most patients who develop pain on the second side, have already had the first side operated on some time previously. However, it does not matter much whether the first side is completely denervated or not, provided the lower part of the face on the second side is not denervated completely also. Olivecrona (1942) has previously mentioned this indication for trigeminal tractotomy, and has even reported a case in which he operated on both sides at one session. My own two cases confirm his report that trigeminal tractotomy can be a satisfactory procedure for bilateral trigeminal neuralgia.

Persistent Pain after Sensory Root Section for Trigeminal Neuralgia.—After a partial section of the sensory root of the Gasserian ganglion, the pain of trigeminal neuralgia may sometimes appear in a part of the face above the denervated area. These cases can then be treated on their merits, either by an operation to extend the section of the sensory root, or by intramedullary tractotomy. They need not be considered further here.

A different problem is the " syndrome of painful anæsthesia " which supervenes in about 3 to 4 per cent. of cases after sensory root section. After a variable period of relief from all pain, these patients develop within the anæsthetic area pain of an incessant dull and often burning character. This pain steadily increases, and before long these unfortunate patients complain as bitterly of their new pain as they did of their old. Grant (1938) and Olivecrona (1939) have both drawn attention to this syndrome, and to the futility of such procedures as further section of the sensory root, thoraco-cervical sympathectomy, and stripping of the carotid artery. Olivecrona (1939) also reported having tried tractotomy in these cases but without success.

It was in therapeutic desperation that I performed my first tractotomies in two typical cases of this syndrome. Both were benefited by lessening of their pain, and this benefit was maintained for several years. If again confronted by this problem, I would again try the same procedure. It is difficult in such patients to tell how completely the descending trigeminal tract has been sectioned, for the face is already analgesic from the previous operation. Guides are afforded, however, by the amount of pain felt by the patient when the tract is actually being sectioned, and also by the appearance of analgesia in areas outside the trigeminal territory. It is interesting that in both my cases pain was produced in the face when the tract was being sectioned, because theoretically the tract should have degenerated as a result of the complete root section performed years before. Perhaps these root sections had not been as complete as was imagined.

Summary

Experiences in twenty patients submitted to section of the descending tract of the trigeminal nerve, and the anatomical principles and technique of the operation, are described. It is recommended that the tract be divided at a level below the lower angle of the fourth ventricle, and that the section be carried out under local anæsthesia, so that resulting sensory loss in the face can be tested and the extent of the incision controlled. A method of confirming the situation of the tract before section by pricking the medulla with a needle is described.

This operative procedure produces loss of pain and temperature sensibility, but with sparing of tactile sensibility, in the skin and mucous surfaces supplied by the trigeminal, facial, glosso-pharyngeal, and vagus nerves. This loss is usually permanent. There is no risk of neuropathic keratitis, facial palsy, or of masticatory paralysis, complications which are not infrequently seen after section of the sensory root of the Gasserian ganglion. The complication most often seen after tractotomy is slight ataxia of the ipsilateral upper limb, but with care this can usually be avoided. Such complications as laryngeal palsy, gross ataxia, and loss of postural sensibility in the ipsilateral limbs will not occur if the incision is correctly placed.

The chief indications for the operation are seen in cases of trigeminal neuralgia involving the first division of the trigeminal nerve, in cases of bilateral trigeminal neuralgia where an operative procedure has to be carried out on the second side, and in cases of severe persistent pain following a previous sensory root section. The procedure is also indicated in some cases of intractable pain due to malignant disease. It is not beneficial in post-herpetic neuralgia.

In the author's experience intramedullary trigeminal tractotomy has passed from being an operation which is still in the experimental stage to being an operation the technique and indications for which have become standardized.

My thanks are due to Miss Evelyn Madigan for technical assistance in the preparation of this paper, and to the various physicians and surgeons who have entrusted me with their patients. With the exception of one patient, operated on in the Radcliffe Infirmary, Oxford, England, through the courtesy of Professor Sir Hugh Cairns, all patients in the series have been operated on in the Dunedin Hospital, New Zealand. I am also grateful to Professor H. Olivecrona and to Drs. F. C. Grant and L. M. Weinberger for permission to reproduce diagrams from their papers.

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CEREBRAL ANGIOGRAPHY: TOLERANCE FOR CONTRAST MEDIA OF DIODRAST TYPE

BY

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Cerebral angiography was introduced by Moniz in 1927. Although increased experience has widened the indications for the method, its general application has been limited because of the difficulty of the injection technique and because of some undesirable results obtained with the use of the contrast media hitherto available.

The operative exposure of the carotid artery limited the application of the method, but this objection has been overcome by the percutaneous technique adopted by Loman and Myerson (1936), which paved the way for a wider use of the procedure (Engeset, 1944 ; Lindgren, 1947 ; etc.).

As all the contrast media available for cerebral angiography are capable of causing complications, it is difficult to determine which should be given preference. The undesirable results obtained with sodium iodide, the first medium used in this method, were avoided later by the use of thorotrast, which was then used extensively. This medium, however, has an irritating effect on the tissues, and in the course of time large injections are liable to give rise to sarcomas, not only in experimental animals, but also in man (MacMahon and others, 1947). Even a small dose involves certain risks, for extravascular deposits of the substance are capable of causing large cicatricial formations and granulomas in the neck (Ziffren, 1940 ; Sjökvist, 1948) of the type that have been known to develop after the use of thorotrast in retrograde pyelography.

It was mainly for these reasons that the use of radiopaque substances of the Diodrast type was adopted for cerebral angiography (Gross, 1939). These substances have proved on the whole satisfactory. They have, however, one inherent disadvantage : they irritate the vessel wall unduly, and this may sometimes cause complications. In two of three cases in which Dyke (1940) used a 70 per cent. solution of Diodrast the results were dramatic, for in one case there developed thrombosis of the common carotid artery, and in the other prolonged loss of consciousness. Collins (1947) was reported to have had a fatal case. The occasional occurrence of epileptic fits, though generally slight, have been reported by Gross (1939), Engeset (1944), Lindgren (1947), and Wickbom (1948).

As thorotrast causes no immediate complications and has good radiopacity, its use is still sometimes recommended in spite of the obvious risks involved (List and others, 1945 ; Govons and Grant, 1946 ; Hodes and others, 1947 ; Hodges, 1947). As, however, the water-soluble contrast media are clearly preferable, the writer decided to investigate the tolerance for contrast media of the Diodrast type, as this question has apparently not been adequately studied.

Since the institution of the Neuro-Roentgenological Laboratory of Lund in 1946, contrast media of the Diodrast type have been used and the tolerance of the patients for these substances closely observed. Our experience is reported here. It should, however, be observed that only the tolerance for the contrast media will be discussed, our material still being insufficient to elucidate the diagnostic value of the method. Those desiring information on this latter subject are referred to Wickbom's (1948) " Angiography of the Carotid Artery."

Material

The material comprises all cerebral angiographic examinations made in 1947 and 1948 by the same technique at the Neuro-Roentgenological Laboratory, Lund, and consists of 277 patients, or 330 cerebral angiographic series. In 31 cases angiograms were made bilaterally. The age of the oldest patient examined was 74 years, and of the youngest 3 years. Ninety-six of the patients were over 50 years old, and 8 were under 15 years. Emergency examinations were made in 21 cases, in most of which the patients were unconscious. The material consisted of 183 patients from the Neurosurgical Department, 73 from the Medical and Neurological Departments, and 21 from other departments.

The conditions which were investigated were: cerebral tumour, 101 (17 of which were not verified, mainly central gliomas); sequelæ of head injuries, 23; vascular lesions, 29; arterial or arterovenous aneurysm, 12; cryptogenetic epilepsy, 29; other neurological states, 71.

Technique

The technique adopted followed that suggested by Lindgren (1947). Usually we take stereoscopic lateral angiograms (each of which requires a separate injection) and also frontal pictures, which means that three injections are necessary for each examination.

As the branches of the internal and external carotid arteries are easily distinguished in stereoscopic angiograms, and filling of the branches of the external carotid artery is often desirable, the injection is usually made by puncture of the common carotid artery. The carotid artery was punctured percutaneously in 323 of 330 angiographic examinations, and in 7 cases the carotid artery was exposed. In 3 cases the patients were examined under narcosis.

The contrast media used were almost exclusively Umbradil (35 per cent.), the diethyl salt of 3·5 diiodopyridone-N-acetic acid, and Umbradil Forte (50 per cent.), a combination of the diethyl salt and the dietanolamine salt of the same acid (supplied by AB Astra, Sweden).

Reactions

Reactions were observed in 21 of the 330 examinations. These do not include those cases of transient pain, brief malaise after the injection, slight allergic symptoms such as a local reddening of the skin, or a few isolated urticarial eruptions.

In 16 cases the patients were slightly febrile (37·6 to 37·8° C.; 99·7 to 100° F.) on the day after examination. The temperature returned to normal after two or three days. A strong allergic reaction was observed in 2 cases. In one of them a marked though brief facial swelling was observed after an injection of 8 ml. radiopaque substance. The reaction in the other case was of a far more serious nature.

A man, 27 years old, had a head injury and lost consciousness. After the accident he suffered from headache, vomiting, and dizziness. Cerebral angiography was carried out on the left side. An injection of 10 ml. Umbradil (35 per cent.) was made into the common carotid artery without any reaction. Three minutes later a second injection was made. Seven minutes after this the patient turned pale and the skin became cold and clammy. The eyelids were markedly swollen. The patient could not speak, and began to gasp for breath. Artificial respiration was carried out and an intravenous injection of calcium was given immediately. After a few minutes respiration was normal, and after ten minutes the patient was able to speak without trouble. The facial swelling subsided quickly, and after forty-five minutes there was only slight œdema of the eyelids and the lips.

In three other cases cerebral angiography was followed by considerable deterioration in the general condition of the patient.

Case 1.—A man of 42 years, who had been languid for four months, on Jan. 13 complained of severe right unilateral headache and numbness of the entire left half of the body. On Jan. 19 the headache, numbness, and langour recurred. Since then the headache had persisted and the patient had become increasingly apathetic. Radiographs of the skull were normal.

Cerebral Angiography.—The common carotid artery was punctured percutaneously, and two injections of 10 ml. Umbradil Forte (50 per cent.) were given with an interval of about three minutes. The films showed that almost all the injected substance had swept through the trunk and branches of the external carotid artery. There was also retrograde filling of the common carotid down to the innominate artery, from where the contrast medium had flowed up into the vertebral artery. The trunk of the internal carotid artery was filled completely with contrast medium for about 1 cm. from the bifurcation. Here a filling defect in the vessel was discerned. A small quantity of the radiopaque substance had passed along the dorsal border of the vessel up to the carotid syphon. In the angiograms made with the second injection the filling defect 1 cm. from the bifurcation of the internal carotid artery was more distinct. The defect was of irregular outline and about 1 cm. long. Beyond it the contrast medium again filled the greater part of the internal carotid artery up to the syphon. Four seconds later the radiopaque substance had passed on through the internal carotid artery and filled the branches of the anterior cerebral artery and the middle cerebral artery. Thus, four seconds after injection the substance had not passed over into the veins but was still manifest in the arteries.

Radiological Diagnosis.—On the radiological evidence a diagnosis was made of thrombosis of the internal carotid artery with considerable slowing of the blood stream in this artery and its branches.

In the evening of the same day a left facial paresis, considerable loss of gross functional power of the left arm, and a left positive Babinski's sign were recorded. The following day the symptoms were more pronounced. No further changes were observed in the patient's condition for about a month, after which he began to recover gradually.

The day after the angiographic examination a temperature of 38·1° C. (100·6° F.) was registered, which afterwards dropped gradually. The temperature did not return to normal until five days after the examination.

Case 2.—A woman of 55 years had acute paresis of the left oculomotorius in April 1948. No other neurologic symptoms were observed. Lumbar puncture showed nothing pathological. The Wassermann reactions in blood and cerebrospinal fluid gave negative results. Plain radiographs of the skull were normal.

Cerebral Angiography.—The left common carotid artery was punctured percutaneously and 10 ml. of Umbradil (35 per cent.) was injected. Three minutes later a second injection of 10 ml. Umbradil Forte (50 per cent.) was made. The contrast filling of the external carotid artery and the internal carotid artery and its branches was good. The branches of the internal carotid were tortuous and of reduced lumen, indicating arteriosclerosis. The rate of flow of the contrast substance did not seem irregular.

About two hours after the examination the patient was mentally confused. She could not follow a conversation. The following day the patient's mind was clear and her general condition was again the same as the day before the examination. The patient's temperature, which had been normal before, rose to 38·4° C. (101·1° F.) on the evening of the examination day. The temperature fell gradually and was normal again on the fourth day.

Case 3.—A woman aged 51 years, since 1944 had suffered from attacks of headache, vomiting, dizziness, and double vision. Since January 1944 there had been a left hemiparesis, and since March 1947 a right facial paræsthesia. During the last six months the patient had become apathetic and her memory was failing. Examination showed disturbance of facial sensation on right side, left facial paresis, paresis of the left arm and leg, homolateral positive Babinski's sign, and bilateral papillœdema of about 3 D. Plain radiographs of the skull were normal.

Cerebral Angiography.—Percutaneous puncture of the right common carotid artery was performed. Two 10 ml. injections of Umbradil Forte (50 per cent.) were given with a three-minute interval. A considerable upward displacement of the vessels of the sylvian group was observed, indicating a temporal tumour. The flow of the radiopaque substance through the internal carotid artery was abnormally slow; even four seconds after injection the substance was still in the capillary phase and not yet discernible in the veins.

After examination the patient became more drowsy and apathetic, while the paresis was accentuated. On the day after the injection the temperature was 38·1° C. (100·6° F.). It fell on the third day, but the patient was still subfebrile six days later, when operation revealed a large cystic astrocytoma in the temporal lobe.

Discussion

The reactions observed after cerebral angiography may be divided into three groups.

Group I.—The characteristic feature of this group is slight fever. This was the only symptom in 16 cases. The temperature rose to between 37·6 and 37·8° C. (99·7 to 100° F.) on the day of the examination or the day after, to return to normal on the second or third day. The most reasonable explanation of this reaction is the formation and absorption of a hæmatoma subsequent to arteriopuncture and in a few, especially in hypertensive cases, palpable hæmatomata were observed. No shortness of breath or other symptoms supervened in these cases. This explanation is supported by the fact that fever developed in one case in which no radiopaque injection was made because a hæmatoma developed in association with the puncture.

It should be observed that the serious reactions seen in Group III were also accompanied by raised temperatures, that were, however, both higher and more persistent than in this group.

Group II.—This group is characterized by a hypersensitivity of the patient to the contrast medium used. Reactions due to such specific allergy are common and result in slight malaise after the injection of contrast media for different purposes (urography, phlebography, arteriography). Small urticarial eruptions are also relatively common. Such marked allergic reactions as in Cases 1 and 2, are, however, uncommon. Nevertheless we know that the allergic reaction is, though rarely, capable of ending fatally, the latest report of such an accident probably being that published by Simon (1948). The best way of avoiding such accidents is to inquire carefully into any history of allergic reactions and to examine for hypersensitivity by means of a small test-injection of the proposed contrast medium. At the Neuro-Roentgenological Laboratory, Lund, the patient is generally given a test injection of 1 to 2 ml. intravenously at least half an hour before the examination proper, and observed for allergic symptoms.

It should, however, be emphasized that allergic reactions cannot be avoided altogether, and that in laboratories where injections of any of these contrast media are made an emergency tray with suitable injection solutions, an intubator, and apparatus for artificial respiration should always be near at hand.

Group III.—This group of reactions, which constitute a type not mentioned previously in the literature, is of great interest. In two of these cases a vascular lesion was diagnosed clinically. On *x*-ray examination a thrombosis of the internal carotid artery was diagnosed in one case, and arteriosclerotic vascular changes in the other. In the third case a large temporal astrocytoma was found at operation. In all three cases the general condition of the patients deteriorated considerably after the angiogram.

The deterioration may plausibly be ascribed to various factors, and need not necessarily be related to the *x*-ray examination. In Cases 1 and 3, for example, the disease had been progressive, so that the condition of the patient might well have deteriorated apart from the puncture and injection.

No direct relation was observed between the angiographic examination and the deterioration. The changes in the patient's condition were not noticed until two to five hours after the injection. This may, however, have been due to the patient's not being observed sufficiently closely immediately after the examination.

If cerebral angiography is suspected to have been a factor in the deterioration, and it probably was, one might reason as follows :

In Case 1, in which thrombosis of the internal carotid artery was diagnosed, it is feasible that parts of the thrombus were torn off in association with the puncture and injection, and carried intracranially by the blood stream into the vascular twigs as emboli. Experience from other cases of thrombosis of the carotid artery and other vascular regions, however, argue against this theory.

In all three cases it is feasible that a vascular disease (definitely present in Cases 1 and 2) or compression of the vessel (Case 1) severely impaired the supply of blood to some parts of the brain, and that the fall in blood pressure and the vasoconstriction regularly following the injection of the contrast medium was sufficient to cause the decompensated circulation in the parts concerned to fail altogether. This explanation is, however, improbable, because with the widespread use of these contrast media in various conditions and in cases with well-established vascular changes, such complications would surely be more common. Nevertheless, the explanation cannot be excluded.

In all three cases the injection was rapid and the contrast media of high concentration. In two cases two injections of 50 per cent. contrast solution were given in rapid succession, and in the other case an injection of 35 per cent. contrast solution was followed by a 50 per cent. solution. The opacity of the vessels in the angiograms indicated that the concentration of the contrast substance in the cerebral vessels was high, and judging by the serial radiographs made at timed intervals the circulation within the region supplied by the internal carotid artery was slowed down in Cases 1 and 2, especially in Case 1. In these two cases the application time of the medium, that is, the time the contrast medium was in contact with the vessel wall, was longer than usual. This prolonged application time may give rise to the assumption that the post-examination deterioration of these patients was due to aggravation of a disorder of the vascular permeability.

In this connexion it would not perhaps be out of place to mention that Broman and Olsson (1948) have demonstrated in experimental animals that contrast media of the Diodrast type are capable of impairing the vascular permeability of the cerebral vessels, that is, of breaking down the blood-brain-barrier, if they are of sufficient concentration and allowed to act upon the vessel wall for a sufficient length of time. In the cat and the rabbit the application time necessary for Umbradil Forte (50 per cent.) to impair the permeability of the cerebral vessels was found to be 5 to 10 seconds. Present investigations seem to indicate that in ischæmia, for example, a lesion may arise in spite of a very short injection time, owing to the fact that the application time is prolonged considerably by the decelerated circulation.

These investigations, based directly on the experience gained from clinical cerebral angiography, argue strongly in favour of the view that in the above-mentioned case the deterioration was due to a disorder of the permeability of the cerebral vessels on account of the contrast medium used. The clinical picture of these cases might well be explained by such a disorder. The changes were slightest and of shortest duration in Case 2, in which also the application time was the shortest and the injection the smallest.

It has also been demonstrated in animals (Broman and Olsson, 1949) that the injurious effect of contrast media of the Diodrast group varies according to the chemical composition of the contrast media, and, strangely enough, also according to the source of supply of media of one and the same composition.

Of the substances tested (Diodrast (Winthrop), Ioduron (Cilag), Dijodon (Leo), Umbradil, Umbradil Forte, and Umbradil-methyl-glycamine (Astra)), the widest margin of safety was provided by the use of Umbradil (35 per cent.), this substance producing no manifest effect on the vessel wall even after so long an application time as 40 seconds. Of the more concentrated contrast solutions, Umbradil Forte proved less injurious than any of the others. In less serious cases the injury passed off within two hours. These animal experiments show that the objections to contrast media of the Diodrast type may be overcome by choosing those substances which, in the pharmacologic tests described above, proved least injurious, and by applying as low a concentration as circumstances permit. If the injection is made into the internal carotid artery, a 35 per cent. solution will always give sufficient radiopacity. If the substance is injected into the common carotid artery, this concentration will almost always allow satisfactory angiograms to be made. Should a 50 per cent. contrast solution occasionally be considered necessary, the patient should be given but a single dose, which should be injected relatively slowly.

In view of the complications liable to supervene immediately after the administration of these

contrast media, and as hypersensitivity can never be definitely excluded, an urgent need for cerebral angiography must occasionally be assessed in the light of the risks involved.

From the above observations it will be obvious that difficulties encountered in cerebral angiography may make severe demands on the examiner, just as the interpretation and critical evaluation of the *x*-ray finding taxes the knowledge and experience of the radiologist. It would seem advisable to assign the use of this method to departments in which there is enough material available for the radiologist to gain experience in cerebral angiography. Examinations, of course, have to be planned, and the results evaluated jointly, by the radiologist and the clinician concerned.

Summary

The tolerance for contrast media of the Diodrast type was studied in three hundred and thirty cerebral angiographic examinations.

Sixteen cases reacted with a slight rise of temperature, two with severe allergic symptoms, and three with cerebral symptoms. These reactions are discussed, and the symptoms of the last-mentioned group are ascribed to a disorder of vascular permeability caused by the contrast medium.

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CEREBRAL TUMOUR CAUSING HYDROCEPHALUS WITH FILLING DEFECT OF THE TEMPORAL HORN

BY

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The important diagnostic significance of filling defects of the temporal horn is well illustrated in the two cases here described. Both patients were middle-aged men with few neurological signs but with raised intracranial pressure and a moderate increase in cerebrospinal fluid cells and protein. In both cases the local cerebral symptomatology indicated a diencephalic disturbance. Ventriculograms showed extensive internal hydrocephalus with no significant lateral shift of midline structures but with filling defects and dislocation of the temporal horn. Although there was hydrocephalus, there was sufficient patency of the fluid pathways to permit the air introduced into the lateral ventricles to fill the fourth ventricle and cisterna magna. In Case 1 (Figs. 1, 2, 3) the deformity of the temporal horn is easily seen ; in Case 2 (Figs. 7 and 8) it is minimal.

Post-mortem examination in both cases revealed ependymoblastoma, which had deeply invaded the brain without causing much displacement. There were numerous secondary deposits throughout the walls of ventricular cavities, with the primary growth in relation to the left temporal horn in each instance, causing the filling defects. Some of the seedlings had caused partial obstruction of cerebrospinal fluid circulation. The deposits which caused obstruction were too small to have been detectable by pneumography.

Case Histories

Case 1.—A man aged 47 years was admitted to hospital on Sept. 11, 1944. For five months before admission he had suffered progressively from headache and from mental deterioration. On admission there was slight papillœdema, tremor of the right hand, and relatively rapid fatigue of the right abdominal reflex. Lumbar puncture revealed a pressure of 210 mm. with normal dynamics. The cerebrospinal fluid was yellow and contained 30 cells per c.mm. (lymphocytes and polymorphs) and 100 mg. of total proteins per 100 c.cm. Ventriculography showed slight dilatation of the lateral ventricles. The significance of a slight filling defect and irregularity of outline of the floor of the left lateral ventricle was not then appreciated.

Within the next year there occurred further mental deterioration, epileptic attacks, increased tremor, and more advanced papillœdema. A second ventriculogram at this time showed a greater degree of symmetrical dilatation of the ventricles than before, and the filling defect of the atrium and temporal horn of the left lateral ventricle (Figs. 1, 2, 3) already mentioned. A rounded dense filling defect thought to represent a tumour in the cerebellar vermis was also noted (Fig. 3 X). Accordingly a suboccipital decompression was carried out in order to relieve the progressive hydrocephalus. Later, despite this procedure, increasing hydrocephalus made it necessary to carry out a third ventriculostomy. Mental deterioration and epilepsy progressed, and the patient died two months later.

Post-mortem examination showed an ependymoblastoma in the left thalamus which had replaced, without displacing, cerebral tissue (Fig. 4). There were multiple secondary tumour seedlings throughout the walls of the ventricular cavities, particularly in the left temporal horn (Figs. 4 and 5). The hydrocephalus was due to a larger seedling on the superior cerebellar vermis (Fig. 6).

Case 2.—A man aged 59 years was admitted to hospital on Oct. 3, 1947. For five months before admission he had been suffering from increasing headache and mental deterioration. Examination on admission revealed moderate papillœdema, tremor, and hypertonia of all four limbs. Lumbar puncture showed a pressure of 90 mm. (lumbar puncture had been performed just before admission, when the pressure was said to be raised), normal dynamics and yellow, clear fluid containing 50 cells per c.mm. (70 per cent. lymphocytes, 30 per cent. polymorphs) and 220 mg. of total proteins per 100 c.cm.

Ventriculography revealed a marked dilatation of the lateral and third ventricles without gross displacement, with a constriction at the upper third of the aqueduct (Fig. 8). The severe internal hydrocephalus due to obstruction of the aqueduct was treated by implacement of ventriculo-cisternal tubes (Torkildsen's operation). The significance of the upward elevation and filling defect of the floor of the temporal horn of the left ventricle (Figs. 7 and 8) was not appreciated. The evidence of previous hæmorrhage and of excess protein in the cerebrospinal fluid and the cause of the aqueduct obstruction remained unexplained. The patient, who was very ill, did not long survive the operation for relief of the hydrocephalic complication.

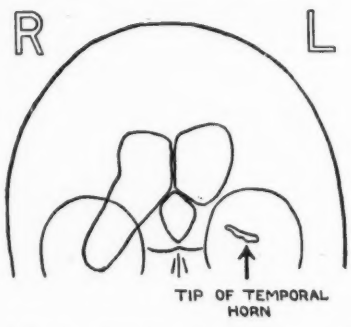

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FIG. 1 (and Key).—Antero-posterior view shows severe hydrocephalus, practically no lateral shift, but filling defect and upward dislocation of left temporal horn (Case 1).

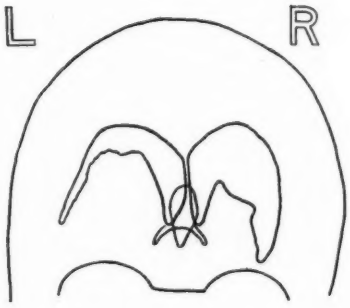

FIG. 2 (and Key).—Postero-anterior view shows very slight shift of septum with filling defect of atrium and filling defect and upward dislocation of left temporal horn (Case 1).

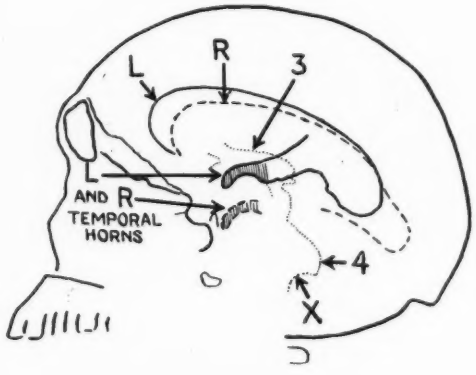

FIG. 3 (and Key).—Left side up. Lateral view shows filling defect and upward dislocation of left temporal horn. L, R, 3, and 4=outlines of left, right, third, and fourth ventricles. X=filling defect in fourth (Case 1).

FIGS. 4 and 5.—Post-mortem sections showing body and temporal horn studded with tumour nodules, and replacement of cerebral tissue by tumour (Case 1).

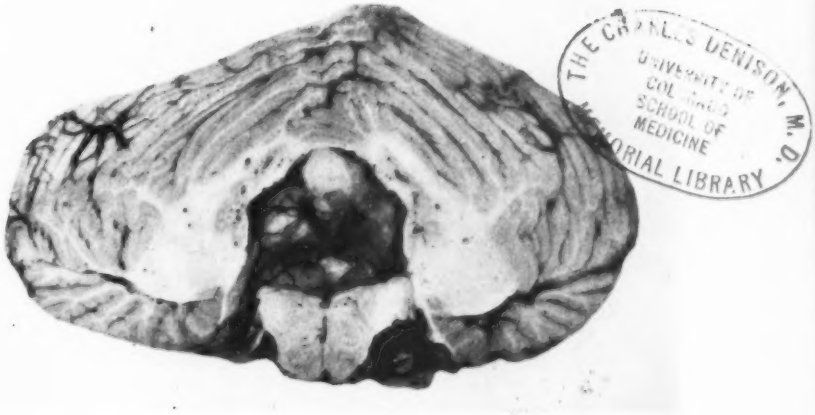
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FIG. 6.—Section showing tumour at superior cerebellar vermis (Case 1).

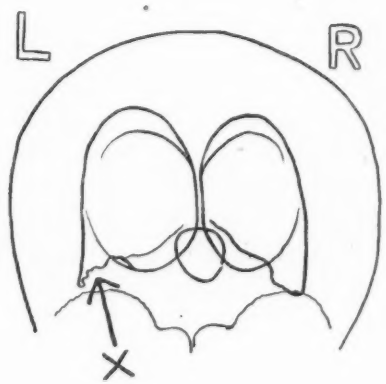
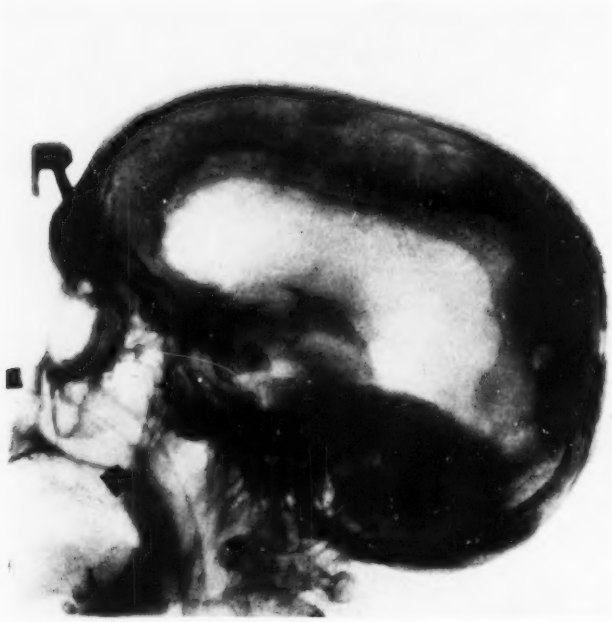


FIG. 7 (and Key).—Postero-anterior view shows absence of lateral shift and gross hydrocephalus symmetrical save for filling defect and slight upward dislocation of left temporal horn (X) (Case 2).



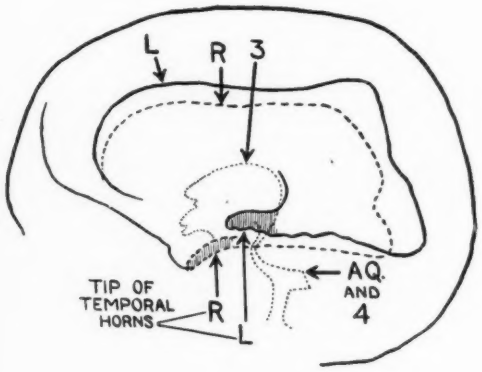


FIG. 8 (and Key).—Left side up. Lateral view shows gross hydrocephalus with filling defect in floor and upward and backward dislocation of left temporal horn. Stenosis of aqueduct can just be made out. L, R, 3, and 4=outlines of left, right, third, and fourth ventricles (Case 2).

FIGS. 9 and 10.—Sections showing body of lateral ventricle studded with tumour and similar deposits in floor of temporal horn (Case 2).

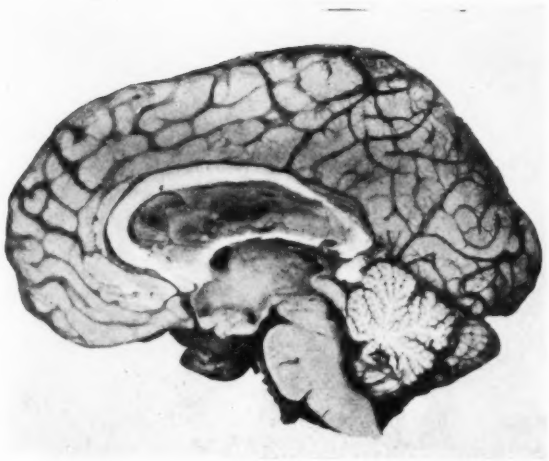


FIG. 11.—Section showing obstruction of lumen of aqueduct of Sylvius by tumour (Case 2).

Post-mortem examination revealed a small ependymoblastoma slightly indenting the floor of the temporal horn of the left ventricle. There were small seedling tumours throughout the walls of the ventricular cavities (Figs. 9 and 10). Some of these in the aqueduct were responsible for the fluid obstruction there (Fig. 11). Death was due to invasion of the floor of the fourth ventricle by other seedlings (Fig. 11).

Discussion

The diagnosis of these neoplasms may be facilitated and the significance of their secondary effects correctly interpreted, if it is borne in mind that the following features may occur in association :

1. Replacement by tumour tissue without displacement may occur, and there may be thus no shift of midline structures even in advanced cases.

2. A gross internal hydrocephalus due to obstruction of the cerebrospinal fluid circulation by seedlings may so dominate the picture that attention may be focused upon the aqueduct and posterior fossa while the supratentorial neoplasm is not noticed.

3. Deliberate search of ventriculograms, if the possibility of filling defect is borne in mind, may reveal plaques and nodules of tumour in the walls of the ventricles.

4. There is usually a moderate increase in the cellular and protein content of the cerebrospinal fluid in the presence of intraventricular ependymoblastoma.

A complete diagnosis may therefore be missed through failure to search for minor filling defects and distortions in the temporal horns in the presence of an apparently symmetrical hydrocephalus. Since we have found these ependymoblastomas highly radiosensitive, their diagnosis is no mere academic exercise but is of great practical importance for adequate treatment of the patients.

The ventriculograms reproduced were from antero-posterior, postero-anterior, and right and left lateral stereoscopic projections. Complete air replacement was first obtained by sitting the patient up and introducing air through both ventricular catheters whilst allowing fluid to escape from a lumbar needle, until air appeared at the latter. The position of the head was suitably altered during the procedure to ensure complete displacement of fluid from the ventricles. Although it was not used in these two cases, and although the abnormalities are sufficiently shown by the method here described, the special filling technique and projections described by Lindgren would probably provide additional information in such cases.

In the series of 137 cases of temporal horn deformity reviewed by Lindgren (1948) the particular syndrome described here does not occur. Certain tumours in his series caused no shift of midline structures, thus " . . . by neurinomas from gasserian ganglion and by pterion tumours growing en plaque, septum need not be dislocated. This is also true of the gliomas. Thus in five cases . . . there has been no displacement of the septum. The same applied to the one case of metastasis and the case of chronic juvenile subdural hæmatoma." He further states, " The pathological process could not have been demonstrated, had not the temporal horn been examined," a statement the value of which is well supported by experience of the two cases here described.

Lindgren's cases of neoplasm without displacement of the septum showed a displacement of the temporal horn. In only three of them were irregularities of the wall present ; these were gliomas. In only one of his cases was hydrocephalus present, and to a minor degree only. We have not previously encountered a description of any comparable cases in which a gross internal hydrocephalus is caused by tumour seedlings, and in which the parent-tumour could be recognized by a critical study of the temporal horn by pneumography.

Summary

A description of two cases of ependymoblastoma with certain ventriculographic appearances.

My thanks are due to Professor Norman M. Dott for his permission to publish these cases and for his advice and criticism in the preparation of this paper.

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RUPTURED CONGENITAL ANEURYSM OF ANTERIOR CEREBRAL ARTERY

REPORT OF A CASE WITH SUCCESSFUL SURGICAL REMOVAL

BY

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This paper describes a case of intracerebral hæmorrhage due to rupture of a congenital aneurysm situated on the right anterior cerebral artery. After a series of acute cerebral vascular incidents the clinical picture was that produced by a rapidly expanding frontal lesion. After full investigation, including air encephalography, the diagnosis of ruptured anterior cerebral aneurysm was made and the aneurysm was successfully extirpated at operation. Dandy (1944) met twenty-five examples of aneurysms involving the anterior cerebral artery and anterior communicating artery, six of which he exposed at operation. In one of these cases he was able to excise the aneurysm, which was arising from the right anterior cerebral artery, after clipping the internal carotid artery.

Case History

A railway worker, aged 47 years, had been suffering rom severe frontal headaches for fourteen days when on April 2, 1947, he collapsed in the bathroom at his home. Although not unconscious, he was dazed and cyanosed, and complained of intense headache and inability to move his left arm and leg. A few minutes later he experienced another severe exacerbation of headache, following which he lapsed into unconsciousness for half an hour.

On admission to hospital he was conscious, complained of stiffness in his neck, and had a left hemiparesis. The blood pressure was 150/90 mm. Hg. The next day (April 3) the hemiparesis was beginning to recover and no other abnormal signs were detected. During the next sixteen days he experienced two transient attacks of severe headache and dizziness, the second attack culminating in unconsciousness for three hours. The blood pressure at this time was 130/90 mm. Hg. In spite of these two attacks the hemiparesis continued to recover. There was no history of trauma to the head.

On May 5, 1947, he was transferred to the Neurosurgical Unit of the Newcastle-upon-Tyne General Hospital, because of persistent frontal headache. By this time the hemiparesis had recovered completely, and the only abnormal findings on clinical examination were bilateral low grade papillœdema and mental slowness in response to questioning. Apart from this, behaviour was normal and he was polite and cheerful. The blood pressure was within normal limits. It was thought that this man had suffered a series of small subarachnoid hæmorrhages possibly due to rupture of a congenital aneurysm, associated with some extravasation of blood into the brain tissue itself. Lumbar puncture on May 13, 1947, suggested previous subarachnoid hæmorrhage: the resting pressure in the left lateral position was 160 mm. of cerebrospinal fluid. The fluid was clear and pale yellow in colour: there were 20 lymphocytes per c.mm. and 60 mg. of protein per 100 c.cm. Culture of the fluid proved to be sterile. (Lumbar puncture had not been performed before admission to the Neurosurgical Unit.) The Wassermann reaction was negative in blood and cerebrospinal fluid.

By May 27, 1947, the headaches had become more severe and the papillœdema had increased; on this date air encephalography was performed by the lumbar route. The radiographs showed slight displacement of the ventricular system to the left, and the presence of two intracerebral cysts filled with air, which were clearly in communication with the anterior horn of the right lateral ventricle (Fig. 1). These cysts were situated in the right frontal lobe of the brain, and had resulted in slight depression of the anterior horn of the right lateral ventricle. The cysts were in communication with each other by means of a narrow isthmus (Fig. 2).

On June 1, 1947, the patient experienced another severe exacerbation of headache. Consciousness was at first unimpaired, but the next day (June 2) headache was severe and the patient developed incontinence of urine and fæces, was drowsy, and became brusque, offhand, and impolite in his dealings with the nursing staff—a complete change from his normal behaviour. The left plantar response by this time had become extensor in type.

A decision was made to explore the right frontal lobe, the preoperative diagnosis being intracerebral hæmatoma following intracerebral hæmorrhage. Although it was impossible to state with certainty the source of the hæmorrhage, it was considered most likely to be due to rupture of a congenital aneurysm situated on the right anterior cerebral artery.

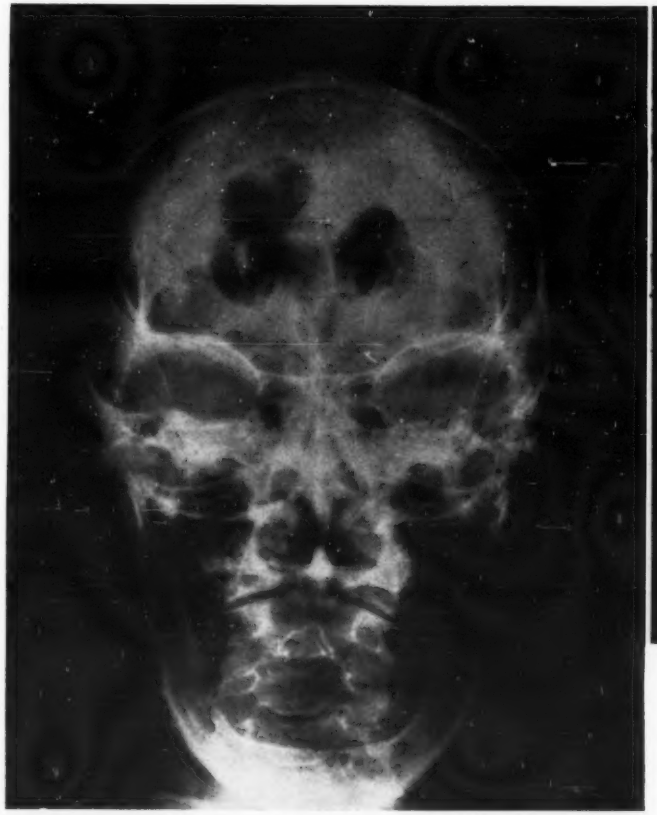

FIG. 1.—Antero-posterior radiograph after air encephalography, to show slight displacement of ventricular system to the left, and the presence of two intracerebral cysts filled with air.

FIG. 2.—Air encephalogram to show the two intracerebra cysts situated in the right frontal lobe, resulting in slight depression of the anterior horn of the right lateral ventricle. The cysts are in communication with each other by the narrow isthmus.

Operation.—On June 5, 1947, under general anæsthesia, a right frontal osteoplastic flap was turned, so as to give adequate access to the right frontal lobe of the brain. The dura mater was tense, and when the right frontal lobe was tapped, the anterior cyst was entered and clear, pale yellow cerebrospinal fluid was released under great pressure. The release of this fluid resulted in a marked reduction of brain tension and the dura mater was then opened. The frontal lobe was incised in order to inspect the interior of the more anteriorly placed cyst. The cyst wall was seen to be lined with grey shaggy material, clearly not tumorous, and since visibility was decidedly poor in the deeper reaches of the cyst, and there was a strong possibility of an aneurysm being present in its medial wall, it was considered advisable to resect the anterior half of the frontal lobe in order to get an adequate exposure. This procedure gave excellent access to the infero-medial aspect of the cyst, and by gentle retraction of the adjacent brain a mass of dark brown altered blood clot was brought into view. This mass of blood clot was projecting upwards and laterally into the cyst from its infero-medial wall. It was roughly hemispherical in shape and approximately one inch in diameter. It was now clear that this clot was capping an aneurysm of the right anterior cerebral artery. The right anterior cerebral artery was exposed proximally and distally to the clot, and silver clips were applied to the artery proximally and distally to the aneurysm ; the aneurysm was then excised. Before the right anterior cerebral artery was clipped, the left anterior cerebral artery was identified and protected with lintine squares. The more posteriorly placed cyst was left undisturbed, since free communication existed between it and the anterior cyst and adequate drainage was therefore possible. After absolute hæmostasis had been ensured the dura mater was closed ; the bone flap replaced, and the scalp reformed in layers without drainage.

The post-operative course was uneventful, the patient being well when he was discharged to his home on June 20, 1947. He has been seen regularly since as an out-patient. He has remained well, and in full employment in his original occupation.

Pathological Report.—The specimen was kept intact and forwarded to the University Department of Pathology, Newcastle-upon-Tyne, and Dr. Greig Thomson reported as follows :

" The specimen is an ovoid structure $2{\cdot}4 \times 1{\cdot}2 \times 0{\cdot}9$ cm. (Fig. 3). The exterior is largely smooth and has a greyish colour, with at one end some brownish staining, presumably hæmosiderin. Section shows an outer wall of red and recent clot 0·2 to 0·4 cm. thick, surrounding a luminated structure 0·5 cm. in maximum diameter containing some blood clot. This is obviously an aneurysm springing from a vessel at the extreme edge of the specimen. The vessel has an external diameter of 0·25 cm., and much of its wall shows yellow atheromatous thickening.

Histological examination indicates clearly that the specimen is an aneurysm. The wall is formed of connective tissue, generally thin, and often old and hyaline, and at one point this appears to be replaced by granulation tissue containing hæmosiderin granules, suggestive of previous leakage. A small amount of muscle is seen in the wall adjacent to the vessel from which the aneurysm springs. About one half of the lumen of the aneurysm

FIG. 3.—Aneurysm removed at operation. The specimen has been sectioned to show the lumen of the aneurysm with clot (left), and its external aspect (right).

is filled with blood clot, most of which is recent, open in texture, and unorganized. Inflammatory changes are absent. In spite of atheroma in the artery bearing the aneurysm, the appearance is that of a congenital type of aneurysm."

Summary

A case is reported of repeated hæmorrhage into the frontal lobe and lateral ventricle from an aneurysm of the right anterior cerebral artery. At operation cysts were found in the frontal lobe, in the base of which an aneurysm and clot were found and successfully removed. No disability resulted from this procedure.

This patient was admitted to the Neurosurgical Unit of the Newcastle-upon-Tyne General Hospital under the care of Mr. G. F. Rowbotham. I would like to express my gratitude to him for permission to undertake the investigation, the operative treatment, and the publication of the case record.

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CLINICAL AND ELECTRO-ENCEPHALOGRAPHIC STUDIES OF PRISONERS CHARGED WITH MURDER

BY

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During the past ten years a number of papers* have been published dealing with the relationship between antisocial behaviour and electro-encephalographic abnormality. The subjects of these enquiries have ranged in degree of behavioural instability from truants to aggressive recidivists in prison, and in ages from childhood to the late forties. With one exception (Gibbs and others, 1945), the results both in studies of children and of adults, suggest a significantly increased tendency for the electro-encephalographic records to be abnormal in subjects whose behaviour has brought them consistently into collision with society. The abnormalities noted are by no means specific, and their incidence ranges from 34 per cent. (Gibbs and others, 1942) to 82 per cent. (Hill and Watterson, 1942).

Since 1942 the opportunity has been taken to record the electro-encephalogram of sixty-four prisoners facing charges of murder; at first the selection of these subjects was governed by the wishes of the prison authorities or of those responsible for the prisoner's defence; but in the past two years the principle has been extended so that the latter part of the present series of cases represents a consecutive unselected sample of prisoners on a capital charge.

Method of Investigation

Full personal and family histories were obtained from each of the sixty-four prisoners, as well as details of the charge and trial proceedings. They were combined in every instance with a routine physical examination, an examination of mental state, and an electro-encephalogram. Subsequently, and before the electro-encephalographic records were studied at all, the cases were assessed on a purely clinical basis in the light of all the available information, and grouped under one of five headings to be described. Finally, in each case, the electro-encephalogram was analysed, and the records grouped and compared with the results of the clinical assessment.

* See starred references.

Clinical Material

The sixty-four prisoners consisted of fifty-eight men and six women. The youngest was a boy of 14 (Case 14), the eldest a man of 60 (Case 54). In not all was the charge of murder proved; in fifteen cases it was reduced to one of manslaughter, and three were found not guilty. Fifteen of the prisoners were ultimately considered to be guilty but insane, insane on arraignment, or insane after a statutory enquiry. Fourteen were executed.

Details of Investigation

The basis of clinical assessment of the five groups of cases was as follows.

Group 1 consisted of cases in which the killing had been incidental to the commission of another crime or had been in self defence. Cases in which harm had been intentional, as for example a blow on the head during a robbery, were not included.

Examples

Cases 47 *and* 63.—Two young men, finding themselves in financial difficulties, decided to break into a shop and steal therefrom any money they could find. They observed the times at which the old man in charge went to lunch, and lying in wait for him on his return they overpowered him and gagged him with a piece of curtain material. After an unsuccessful search for money they left the shop hurriedly and the old man was found some hours later suffocated by the gag.

Case 62.—A young man had separated from his wife following frequent quarrels with her because of her allegedly immoral life. He met her one day in the street, a quarrel ensued and she attacked him with a knife. In the struggle which followed she was stabbed in the chest and died.

Group 2 included all cases in which it was considered that there was a clear motive for killing or in which death followed intended violence during the commission of another crime.

Examples

Case 32.—A young soldier, returning home after more than a year overseas, found his wife in a maternity

hospital about to be confined. When he visited her, accompanied by her mother and sister, she ignored him completely and refused to speak to him; he asked to be left alone with her for a short time and then strangled her.

Case 43.—A man of 50 years of age, who had always been a heavy drinker, was constantly being nagged because of this by his wife. One evening she was particularly critical and had been chiding him all night. As he returned from the lavatory he noticed a hammer and seizing it he struck his wife several blows on the head which resulted in her death.

Group 3 included those cases in which the crimes were apparently motiveless or in which the motive was very slight.

EXAMPLES

Case 1.—A young man of 25 years of age had been keeping company with a girl of his own age for some time. He had an exemplary war record and the couple were on the very best of terms. There had been occasional sexual intercourse and no major quarrels. On one occasion, for no apparent reason, he had seized her by the throat but had relaxed his grip without harming her. She had agreed to forget the incident and to continue their acquaintanceship. On the night of the murder they had spent the evening together listening to the radio at his home. No sexual relations had taken place nor had any sexual advances been made. As the girl rose to go he suddenly seized her by the throat and strangled her, placing the body under the bed and then notifying the police.

Case 10.—A countryman of 26 years of age had been associating with an Irish domestic servant as a result of which she became pregnant and gave birth to a child. He was in love with the girl and wished to marry her but there were religious differences. They continued to discuss arrangements amicably and it was agreed that though they would marry in the Roman Catholic Church he would not change his religion. Having met the girl one evening to discuss marriage arrangements, he suddenly and without any warning felled her with a heavy piece of wood and stabbed her in the neck with his clasp knife.

Group 4 consisted of those persons who were charged with murders in which there was a strong sexual element; only those cases were included, however, in which sexual activities of some kind occurred actually at the time of the murder.

EXAMPLES

Case 38.—A young sailor, much the worse for alcohol, accosted a much older woman and sexually assaulted her in a lonely spot. Her body was found as it had been left at the time of intercourse and she was found to have been strangled. She had also been robbed but most of the articles taken had been subsequently discarded indiscriminately.

Case 55.—A man aged 31 years had a paramour of 48 years, a widow with an adult daughter and adolescent son. Following one of his visits to the house the three occupants were all found strangled. Both women were naked and showed signs of sexual interference; in the case of the younger woman intercourse had apparently occurred after death and her pubic hair had been violently torn out. The boy was badly mutilated and his genitals had been amputated and placed in his mother's mouth.

Group 5.—The last group consisted of those persons who were found unfit to plead or guilty but insane at their trials or who were subsequently found to be insane at a Statutory Enquiry. One case (Case 10) was included in Group 3 rather than in this group because no evidence was given at the trial that he was insane and there was no suggestion at any time during the period of observation that he was insane. As the result of an eloquent speech by his counsel, however, a sympathetic jury found him to be guilty but insane.

EXAMPLES

Case 39.—A young man had not felt well and refused to go to work. His mother rebuked him and he felled her with a flat iron and carried her body to the cellar. On reception he was confused, depersonalized, and had delusions of persecution. There was thought-blocking and poverty of affect and he was a clear case of schizophrenia.

Case 11.—A young man of 28 years was received in a state of excitement and suffering from delusions that he was being drugged and that all his strength was being drawn out of him through his penis. He thought that his uncle was responsible and he killed him with a flat iron. Whilst under observation he had many epileptic attacks which were followed by excitement and confusion.

On the basis of this grouping the 64 cases under consideration were divided as follows:

	Cases
Group 1	11
Group 2	16
Group 3	15
Group 4	8
Group 5	14
Total ..	64

Investigation of Electro-encephalograms

The electro-encephalograms (EEG) were obtained mainly with a Grass 3-channel standard electro-encephalograph using ink-writing oscillographs, although a few of the cases were examined with an Ediswan 6-channel apparatus. Bipolar electrodes were used in all cases, records being obtained from serial positions in antero-posterior and transverse planes of the head. All subjects were examined after twelve hours' fasting. The total recording time

was never less than thirty minutes. At the end of the recording, each subject was induced to overbreathe for a further period of three minutes, and, in the event of significant alteration in the E.E.G., blood was taken for estimation of the sugar concentration. The subject was then given 100 g. of glucose by mouth and the overbreathing test repeated after thirty minutes, the blood sugar level being again estimated. In the assessment of results, the E.E.G. response to overbreathing was not by itself considered significant as a criterion of abnormality. The E.E.G.s have been divided into four groups, reflecting the degree of abnormality. These have been called " normal," " mild unspecific," " severe unspecific," and " specific, focal, or epileptic abnormality."

Normal Electro-encephalograms.—E.E.G.s have been classified as normal under the following circumstances. A dominant frequency of 8 to 13 c/sec. present in the post-central areas of the head, which tends to " block " to visual attention stimuli, such rhythm being present from 5 to 100 per cent. of the time and symmetrical on the two hemispheres in respect to frequency, amplitude, and spread; however, slightly greater spread and amplitude of this rhythm on the right side was accepted as normal in young persons. Activity at 14 to 30 c/sec. of low voltage, having symmetrical distribution and appearance in the precentral areas was often present. No record was regarded as normal within the age range studied in which activity at less than 4 c/sec. was seen as a discrete rhythm. A small amount of activity at 4 to 7 c/sec. in the central and temporal areas, particularly in a transverse electrode placement was accepted as normal provided such activity did not constitute the dominant activity in the record, and was not seen to have paroxysmal occurrence or to have an amplitude exceeding that of the 8 to 13 c/sec. activity seen in the same part of the record. As already stated the response of the E.E.G. to three minutes' overbreathing was not alone considered as a criterion, provided such changes as occurred were symmetrical on the two sides in respect to frequency, amplitude, and spread, and, of course, provided no specific epileptic wave forms appeared (see below). However, the marked development of high voltage slow wave activity at high levels of blood sugar (more than 130 mg. per cent.) constituted a criterion of abnormality of the mild unspecific type (Heppenstall, 1944).

Mild Unspecific Abnormal Electro-encephalograms.—Records in which, in addition to the normal appearances of 8 to 13 c/sec. activity in the postcentral areas, and possibly 14 to 30 c/sec. activity in the precentral areas, other activity was present, in most instances rhythms in the 4 to 7 c/sec. range, but in excess of that seen in the " normal " group. Records in which rhythm of this frequency (theta) dominated the traces from the frontal, central, or temporal areas were included in this group.

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E.E.G.	Group					Total
	1	2	3	4	5	
Normal	10	12	4	4	2	32
Mild unspecific ..	—	2	5	3	7	17
Severe unspecific ..	1	—	4	—	2	7
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Results

The results of the electro-encephalograms in each of the five groups are shown in Table I.

Table II gives more detailed results, showing individual cases and indicating any significant family or personal history, together with the final verdict and disposal.

A study of the results indicates at once the preponderance of normal over abnormal E.E.G.s in Groups 1 and 2, whereas in the case of unmotivated crimes (Group 3) the reverse holds good. The only subject in Group 1 (47) who had a severe unspecific abnormality in his E.E.G. was a man of 22 years of age who had suffered in childhood from osteomyelitis of the left arm, thighs, and ribs and had been severely incapacitated thereby. He was sensitive about his disability and of very immature personality. The E.E.G. was, in fact, the type which might have been found in an unstable adolescent. Two of the abnormal E.E.G.s in Group 2 were specific in character. Case 53 had a history of head injury on two occasions and the E.E.G. showed a focal abnormality in the left hemisphere. Case 46

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TABLE II

DETAILS OF CASES IN THE SERIES

Case	Age	History		E.E.G.	Disposal
		Family	Personal		
			Group 1		
6	28	F. Alc.	—	Normal	N.G.
9	51	—	—	Normal	Mans.
20	20	—	—	Normal	G.Ex.
26	35	B. Migr.	? Epil.	Normal	Mans.
40	21	—	Hd. inj. at 20	Normal	G. Rep.
47	22	—	—	Severe Unspec.	Mans.
51	22	F. Alc.	—	Normal	G. Rep.
54	60	B. Sui.	Alc., ? Epil.	Normal	Mans.
59	29	—	—	Normal	Mans.
62	22	—	—	Normal	N.G.
63	29	—	Severe Hd. inj. at 27	Normal	Mans.
			Group 2		
4	40	—	" Fits "	Normal	G. Ex.
16	41	—	—	Mild, Unspec.	G. Rep.
18	53	F. Alc.	Alc.	Mild, Unspec.	Mans.
19	21	—	—	Normal	G. Rep.
21	33	—	Hd. inj.	Normal	G. Ex.
29	19	—	Syphilitic	Normal	Mans.
32	24	—	—	Normal	Mans.
42	34	—	Hd. inj. and fits	Normal	Mans.
43	49	U. Alc.	Alc.	Normal	G. Rep.
45	27	—	Minor Epil.	Normal	G. Ex.
46	23	F. Alc.	Hd. inj. and Epil.	Specific Epil.	G. Rep.
50	36	—	—	Normal	G. Rep.
52	31	—	Hd. inj. at aet. 12	Normal	G. Rep.
53	34	G/m Ins.	Two Hd. inj. to left hemisphere	Specific focal	G. Ex.
58	34	—	—	Normal	G. Ex.
64	—	—	—	Normal	G. Ex.
			Group 3		
1	25	G/f Sui., 2 S.s ins.	—	Mild, Unspec.	G. Rep.
3	22	—	—	Normal	Mans.
8	18	—	Polio.	Mild, Unspec.	Mans.
10	26	—	Cereb. f.	Normal	G.I.
12	23	G/f Sui., F. Alc.	Attempted Sui.	Severe, Unspec.	G. Rep.
14	14	—	—	Normal	G.H.M.P.
15	27	M. Migr.	Alc.	Severe Unspec.	Mans.
22	29	—	Epil.	Specific Epil.	Mans.
25	16	—	—	Severe, Unspec.	G.H.M.P.
27	23	Two B.s df. & db.	—	Severe focal	N.G.
30	20	M. Epil., F. Alc.	Hd. inj. to temporal lobe, Men. Hos.	Mild Unspec.	Mans.
31	22	—	—	Mild Unspec.	G. Ex.
36	39	—	" Blackouts "	Normal	G. Ex.
49	24	—	" Blackouts "	Mild, Unspec.	G. Rep.
56	29	F. convulsions	Hd. inj., fits and petit mal	Severe Unspec.	Unknown
			Group 4		
5	26	F. Alc.	Alc., ? Epil.	Specific Epil.	G. Ex.
7	22	A. Ins.	Alc.	Mild, Unspec.	G. Ex.
13	16	—	Epileptiform fits	Mild, Unspec.	G. Rep.
24	29	—	—	Normal	G. Ex.
37	24	—	Hd. inj. at 10 and Epil.	Normal	G. Rep.
38	23	—	—	Mild, Unspec.	G. Ex.
44	21	G/m and U. Ins.	—	Normal	G. Rep.
55	31	—	Hd. inj. and ? Epil., Alc.	Normal	G. Ex.
			Group 5		
2	25	—	1936 certified M.D. 1944 attempted Sui.	Severe Epil.	G.R.I.
11	28	—	H.I. at 4	Specific Epil.	G.I.
17	48	F. Ins.	—	Mild, Unspec.	G.R.I.
23	32	—	Attempted Sui. aet. 22	Mild, Unspec.	G.I.
28	27	S. and B. Epil.	Minor Epil.	Mild, Unspec.	G.I.
33	30	M. Ins.	Always unstable	Mild, Unspec.	G.I.
34	20	F. Alc., A. Epil.	Hd. inj.	Mild, Unspec.	G.I.
35	—	S. Ins.	Epil. colony	Severe, Unspec.	I.A.
39	25	Two B.s Alc.	—	Mild, Unspec.	G.I.
41	24	—	—	Mild, Unspec.	G.R.I.
48	24	F. Ins. and Epil.	Hd. inj. and Epil.	Specific Epil.	G.I.
57	59	—	—	Normal	G.I.
60	26	F. Ins., M. Unstable	Always abnormal	Severe, Unspec.	G.I.
61	25	—	Twice in Mental Hospitals	Normal	G.I.

Abbreviations :

F. = Father.
M. = Mother.
G/f. = Grandfather.
G/m. = Grandmother.
B. = Brother.
S. = Sister.
U. = Uncle.
A. = Aunt.
Alc. = Alcoholic
Cereb. f. = Cerebrospinal fever
Epil. = Epilepsy
Hd. inj. = Head injury
Ins. = Insane
Migr. = Migraine
Polio. = Poliomyelitis
Sui. = Suicide
G. Ex. = Guilty and executed
G. Rep. = Guilty but reprieved
N.G. = Not guilty
Mans. = Reduced to manslaughter or infanticide
G.I. = Guilty but insane
G.R.I. = Guilty but reprieved and certified insane
G.H.M.P. = Guilty and detained during His Majesty's Pleasure because of age
I.A. = Insane on arraignment.
Unspec. = Unspecific
Df. & Db. = Deaf and dumb

suffered from traumatic epilepsy and had a specific epileptic E.E.G. Two other subjects (Cases 16 and 18) had mildly abnormal unspecific E.E.G.s, and it is interesting that in each case the murders had very poor motives and might possibly have been included in Group 3. One murdered a prostitute, allegedly because she stole his wallet, though at the trial it was suggested that he had robbed her ; the other murdered his paramour on the flimsiest of pretexts of jealousy. Reconsideration of the four men with normal E.E.G.s in Group 3 (Cases 3, 10, 14, and 36)

TABLE III

		Record	
		Normal	Abnormal
Epilepsy	5	0	5
Schizophrenia	3	1	2
Depression	3	1	2
Psychopathic personality	2	0	2
Paranoia	1	0	1

did not reveal that they had been misplaced in the group, for in every case the murder appeared to be completely without motive of any real strength.

While results in Group 4 may be too few for significance, the eight cases being equally divided between normal and abnormal, Group 5 showed a very high proportion of abnormal records. In order better to appreciate the type of cases encountered in Group 5, the final diagnoses are given in Table III.

Discussion

The marked preponderance of abnormal records in Groups 3 and 5 (73 per cent. and 86 per cent. respectively) suggests strongly that whatever the nature of the cerebral dysfunction which such abnormal records indicate, it is significantly correlated with a capacity to commit violent acts of an apparently motiveless character. These cases include not only aggressive psychopaths such as Case 31, a man of 22 who battered to death with a hammer a woman who asked him to stop fooling about with the lights, following this by killing with the same hammer the child of his victim, both murders taking place in the presence of his wife ; they include also individuals who are clinically apparently perfectly normal : Case 1, already quoted as an example of Group 3, being one. In both these cases the abnormality of the E.E.G. was regarded as unspecific but definite. It is of interest that Group 3 cases as a whole exhibit a higher percentage of abnormal records even than Hill and Watterson's (1942) aggressive psychopaths. The still higher proportion of abnormal records in Group 5 may be accounted for by the fact that five of them were epileptics and a further two grossly aggressive psychopathic personalities, with characteristic records.

In contrast, Group 1, the " accidental murder " group contains less than 10 per cent. of abnormal records, approximating closely to the proportion found in the general population (Williams, 1941), while Group 2—the motivated group—contains 25 per cent. of abnormal records which may correspond to the 34 per cent. found in a group of one hundred unselected criminals by Gibbs and others in 1942, and to the 31 per cent. quoted by the same writers for the murderers in this group after they had enlarged it by selection to include seventy-five men convicted of this crime. It compares also with the figure of 26·7 per cent. for the normal prison population given by Silverman (1943).

Rosanoff (1943), in a clinical study of thirty consecutive cases of men convicted of murder, diagnosed no fewer than fourteen of them as psychopaths. A study of his case histories reveals that the thirty would have fallen under our five group headings as in Table IV.

TABLE IV

GROUPING OF ROSANOFF'S CASES

		Psychopaths	Total
Group 1 or Group 2	" Desperate, motivated, or possibly accidental killings "	8	18
Group 3		2	3
Group 4		1	2
Group 5		3	7

It is, however, necessary to point out that Rosanoff defines psychopaths for this purpose as " so called habitual (or) professional . . . offenders." This is a definition so wide and general as to be of questionable value.

Conclusions

While it is generally acknowledged that unspecific abnormalities in the E.E.G. of a particular individual divorced from the relevant clinical picture and history, are valueless from a prognostic standpoint, there is another way of dealing with the evidence of investigations such as the one just described which may have more practical value.

The unsatisfactory nature of the psychiatric criteria commonly admissible in criminal justice for the assessment of an individual's culpability is well known ; moreover such assessment has ultimately to be made by a collection of laymen—the jury—rather than by a trained observer. The courts are

TABLE V

FATE OF CONVICTED PRISONERS IN THIS SERIES

	Guilty and executed	Guilty and reprieved	Not guilty	Reduced to manslaughter	Guilty but insane	Insane on arraignment	Guilty but reprieved and insane	Guilty and H.M.P. (under 18)	Untraced
Group 1 ..	1	2	2	6	—	—	—	—	—
Group 2 ..	6	6	—	4	—	—	—	—	—
Group 3 ..	2	3	1	5	1	—	—	2	1
Group 4 ..	5	3	—	—	—	—	—	—	—
Group 5 ..	—	—	—	—	10	1	3	—	—
Total ..	14	14	3	15	11	1	3	2	1

concerned, not with insanity as such, but with criminal responsibility (Kenny, 1936). Yet the possibility that in the E.E.G. we have at least an objective indication of innate propensities affecting responsibility—an indication moreover which is likely to be of maximal value in precisely those cases where clinical observation and the operation of reason are least able to elucidate the basis for the individual's actions—is one worthy of serious consideration. These cases may display no clinical evidence of insanity—either legal or medical—whatever, yet unless, as seems highly unlikely, the correlation between apparently motiveless violence and an abnormal E.E.G. is purely coincidental, they are the very subjects who most of all require further investigation and study over a prolonged period, as well as detention for the protection of the community.

What, in fact, happened to those included in the present series may be seen from Table V, which is abstracted from the data included in the comprehensive Table II.

At a time when the public conscience is stirred over the issue of capital punishment, the potential value of the electro-encephalogram in providing the basis for a more enlightened attitude towards at least one group of criminals should not be underrated.

Summary

A clinical and electro-encephalographic study of sixty-four prisoners charged with murder suggests that a significant correlation exists between apparently motiveless crime and electro-encephalographic abnormality. While this abnormality is not specific, it has been found in over 70 per cent. of prisoners whose crimes appeared motiveless but who were otherwise clinically sane and normal. The indications for further investigation of convicted prisoners falling into this group, and for their preventative detention, are discussed.

We are indebted to Dr. Denis Hill for access to material in his Department of Applied Electrophysiology in the Institute of Psychiatry, Maudsley Hospital, and for his analyses and comments on the original records; also to the Prison Commissioners for facilities for carrying out the investigation and for permission to publish it when completed; to Mr. A. Lubin for evaluation of statistical data, and finally to Professor Aubrey Lewis, under whose auspices on behalf of the Nuffield Foundation the work of one of us (D.S.-C.) was performed.

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BOOK REVIEWS

Sir William Gowers—1845–1915. A Biographical Appreciation. By Macdonald Critchley. 1949. Limited Edition. William Heinemann, Ltd. Price 17*s.* 6*d.*

The name of Sir William Gowers, like that of his great contemporary, Dr. Hughlings Jackson, is known to neurologists all the world over. But while Jackson's contributions have attracted increasing attention with the passing of the years, the many outstanding achievements of Gowers have not perhaps received their full measure of recognition. To compare these two great men is, however, as the author truly writes, "a vain pursuit for they were so different in turn of thought, in culture and in temperament." A biography of Sir William Gowers, "who has contributed more than any other to the study of nervous diseases," was much to be desired and is very welcome. Macdonald Critchley is to be congratulated for he has produced an admirable description of the personality of, and the contributions to knowledge by, a brilliant clinician. His biography will be read with keen interest and appreciation by the few who recall Sir William, and will intrigue all who profess to follow the specialty in the elucidation of which Gowers was such a prominent pioneer.

William Gowers was brought up in humble and straitened circumstances. His father died when he was eleven; he left school at fifteen, and was then attached as an apprentice for two years to a local medical practitioner, when his chief duties were to dispense medicines and drive the doctor's gig. Even in his early days he was evidently an assiduous worker for in 1863, the year he passed his London matriculation, he wrote in his diary "I fortunately woke about five . . . did mathematics until nearly 6.30 and a little of an Ode of Horace, and then German until breakfast." When an undergraduate he acquired a knowledge of shorthand, the value of which he so persistently advocated in after years. Botany and chess were at that time his chief recreations. He became, too, a skilful draughtsman, though he never had a lesson, and he was in later life a talented etcher.

After a very distinguished undergraduate career, he acted as assistant and secretary to Sir William Jenner. Perhaps it was Sir Russell Reynolds who, in Gowers' student days at University College Hospital, directed his attention to neurology. Appointed Registrar to the National Hospital for the Paralysed and Epileptic in 1870, he was elected an assistant physician to University College Hospital two years later. Gowers' name is so closely associated with neurology that we are apt to forget that he held the Chair of Medicine at University College (but resigned in 1888), wrote several short papers on general medicine, and invented his hæmoglobinometer which was for so long in general use. Was it this early experience which prompted him occasionally to say, "The neurologist must be a specialist, he cannot be an exclusivist"?

A brief reference to the scope of neurological practice in the seventies, a photograph of the distinguished Staff of the National Hospital in 1887, and a note on the respective ages of the leading neurologists in this country and overseas in 1880, when Gowers was thirty-five, are of much interest. All who remember Sir William Gowers will recall "the glint of his ice-blue eyes," his harsh strident voice, and his caustic speech. His manner was rather cold and aloof, he often withheld praise, was sometimes intolerant, and was admired rather than liked by his colleagues. But for Hughlings Jackson and his achievements he had a deep regard and admiration, and when the bust of his senior colleague was unveiled in the Hall of the National Hospital, Gowers, who delivered an address, referred to him as "our Master." Yet despite his somewhat unattractive personality, Gowers was a satisfactory chief to work for; his house-physicians learned much from him, he showed an appreciation of their efforts, and he gave due credit to those who served him well.

A scholarly epitome of some of Gowers' activities and a few of his more important contributions to the literature from 1872 onwards is engrossing. Elected a Fellow of the Royal College of Physicians and appointed Goulstonian Lecturer in 1879, he selected epilepsy as his subject. His book on epilepsy appeared some years later; and a second edition in 1901, based on some 3,000 personally observed cases, remains a classic to this day. In 1878 he also published his "Diagnosis of Diseases of the Spinal Cord," a "Monograph on Pseudo-hypertrophic Paralysis," and a "Manual of Medical Ophthalmoscopy." These were but a foretaste of what was to come from his pen in the years that followed. There are, indeed, few aspects of neurology to which he did not add his quota and illuminate. A complete bibliography is an invaluable addition to the volume. Gowers' name is especially associated with his "Manual of Diseases of the Nervous System"—his *magnum opus*—the first volume of which appeared in 1886, the second in 1888. Translated into several European languages, it may well be called "the Bible of Neurology." "Anyone who thinks he has stumbled on something new should not neglect to search the Manual before claiming originality." How true it is that "almost all the bricks and mortar of this edifice were culled from his own case notes and clinical memory." Even the illustrations were original, for they were drawn by his own hand.

"As a neurologist Gowers' role was that of an accurate diagnostician and a teacher"; he relied on close application, keen observation, a brilliant memory, and painstaking physical examination; he did not compile data from the published work of others; he did not employ the methods of experimental investigation; he was able to pick out a species which had not previously been described or labelled; he took elaborate shorthand notes of all his cases, and filed special lists of the unusual or the bizarre. Among Gowers' contributions to neurology, we all recall the tract in the spinal cord known by his name, that it was he who introduced the term "knee jerk" and he who diagnosed the tumour of the spinal cord, which was removed by Horsley in 1888—the first operation of the kind recorded in the literature. But these are *inter alia* isolated items, for Gowers' chief contributions which are here referred to may be described as "the recognition of a number of salient, novel and important clinico-pathological features culled from his experience." He had a literary style which was distinguished, simple, arresting, and clear. As a teacher he was "brilliant, stimulating, interesting, informative," and his teaching clinics were thronged.

The author in a concluding sentence pays fitting tribute to a great Master when he writes " We may close with the challenging statement that William Gowers was the greatest clinical neurologist of all time."

Neurology. By Roy R. Grinker and Paul C. Bucy. 1949. Blackwell Scientific Publications. Pp. 1138; 393 illustrations. Price 63s.

This American textbook of neurology has much to commend it. Dr. Bucy has now become joint editor, and his influence, especially on the sections concerned with neuroanatomy, neurophysiology, and cerebral tumours, has made the book more up-to-date and useful than many current textbooks of neurology. It is of course easy to find something to criticize in a textbook; for example, the sections on some of the more medical aspects of neurology, such as the section on poliomyelitis, are somewhat uninspired. Many of the views expressed regarding head injuries will not be accepted by most students of this form of trauma. The suggestion on p. 834 that basal skull fracture with facial paralysis should have the nerve explored is unfortunate, for recovery in this type of injury is almost invariable unless otitis media supervenes. However, this textbook will be found to be a mine of information, most of which is reliable and remarkably up-to-date. Most of the numerous illustrations are excellent.

Atlas of Neuropathology. By Wm. Blackwood, T. C. Dodds, and J. C. Sommerville. 1949. Edinburgh: E. and S. Livingstone. Pp. xi + 199, with 262 figures. Price 35*s*.

There is, at the present time, a very definite need for a good atlas of neuropathology and at first glance this beautifully produced book appears to fill the gap. It is designed to present to clinicians or pathologists the most important pathological conditions in a clear and simple way. Many of the illustrations are of the highest quality, but a few fail adequately to illustrate the lesion they are supposed to show. The main faults in the book are the overcondensed descriptions of the pathological conditions illustrated, and the unnecessarily lavish layout, which has made it more expensive than it need be. Carbon monoxide poisoning, described in fourteen lines of letterpress, is illustrated by five figures and the whole occupies four pages. It would be an improvement to show and describe the condition on two pages.

It is to be hoped that when a second edition is called for there will be less space wasted, and that more illustrations of common conditions will be given. The bibliography of thirty-seven items contains five references to muscle and three to Wernicke's encephalopathy, but none to the classical papers on disseminated sclerosis. It is to be hoped that a more representative and useful bibliography will be prepared for the next edition.

Pathology of the Nervous System. A Student's Introduction. By J. Henry Biggart. 1949. Edinburgh: E. and S. Livingstone. Second Edition. Pp. xii + 352, with 232 figures and 10 colour plates. Price 21*s*.

The second edition of this excellent little book retains the same plan as the first, though there has been a good deal of revision. The author's intention has been to " help the student to apply the general principles of pathology . . . to the lesions of the nervous system," and in this he has in general been successful. Rare and obscure conditions receive only passing notice, and the bulk of the book is devoted to common and important pathological conditions. The illustrations are well chosen and are of a high quality.

One feature of the book is disappointing and suggests a hurried revision. Recent papers which are referred to in the text are not added to the short bibliographies at the ends of the chapters. This is a pity, since the student who is given the date of a paper with no journal reference is even less likely to look it up than he would be if a complete reference were given. Nevertheless, this book can be strongly recommended to students and to those who undertake the thorny journey which leads to specialization in neurology, neurosurgery, and psychiatry.

Verstehende Psychologie (Erlebnislehre). By Hans W. Gruhle. 1948. Stuttgart: Georg Thieme. Pp. xii +622. Price RM.30.

This " textbook," as the author himself calls it, is really a noteworthy contribution to our knowledge and understanding of a branch of psychology which is little studied, the psychology of " understanding " and of empathy. In the first part an outline is given of the " psychology of experience," and its materials and methods are presented. The second larger part shows the wide field of its possible applications, in the humanities such as history, education, social science, and the arts and jurisprudence, as well as in biology and medicine. Gruhle's intention is not to establish a new psychological theory, or to found a new school, but to explore those psychological phenomena which in his view cannot be dealt with by the methods of natural science with their dominant aim towards quantification. Psychic functions which are only realized by inner experience, such as consciousness, volition, the self, thinking, imagery and emotions, are beyond the reach of such methods. Gruhle does not deny the value of an approach " from outside " along the lines of behaviourist experiment, the physiology of sensation and perception, electrophysiology, and neuro-anatomy. These methods have contributed much and will contribute more to the progress of psychological knowledge. But he is concerned with the central core of phenomena, the focus to which all these methods of approach are directed. The phenomena are directly known to each of us in our inner experience; their study is what Gruhle calls pure psychology.

There is nothing mysterious about this psychology. On the contrary, its facts are tacitly assumed in any theory of psychology. They are described in Gruhle's book as they are empirically ascertained, and in lucid and simple language. Psychological experience of this kind is communicated from man to man, and not only by the roundabout method of self-description; this leads to the problem of psychological understanding and empathy. The study of expressive movements, gestures, physiognomics, physical appearance, and the varieties of bodily constitution can then be discussed. The various ways we formulate our ideas about character, temperament, intelligence, and personality are described and criticized; and the first part of the book concludes with a discussion of the influence of psychological experience on man's personal environment and the shaping of his life.

In the second part no offer is made to historians, philologists, social scientists, and educationists to solve all their problems by psychology. On the contrary, Gruhle pays a tribute to the value of the special modes of approach peculiar to each of these sciences. But he does indicate how many of their problems are human problems, demanding the collaboration of psychology; and he shows how small is the extent to which psycho-

logical knowledge and ideas have been used. The author's profound knowledge of the literature of many branches of science and the humanities is used to illuminate a wide field of facts. It makes this work a unique treasure of psychological information drawn from all possible sources. Eighteen pages of references and an excellent index of persons and subjects add to the accomplishment. This volume, which was written during a period in which the author was dismissed by Hitler from his post as an academic teacher, is the product of a courageous, clear, and critical mind, combining scholarship with the wisdom of an experienced physician.

Prognose und Therapie der Geisteskrankheiten. Second Edition. By Max Müller. 1949. Stuttgart: Georg Thieme. Pp. viii plus 209. Price DM. 16.50.

The first edition of this work appeared in 1935, so that the second has had to be entirely re-written in order to provide an account of the major methods of physical treatment of the psychoses which have appeared since that date. In the first part of the book prognosis and treatment are discussed in a general way; the indications and the methods of individual and group psychotherapy, fever therapy, insulin treatment, convulsive therapy, continuous sleep, and prefrontal leucotomy are dealt with systematically and comprehensively. In the second part of the book, schizophrenia, manic-depressive psychoses, syphilis, epilepsy, and toxic psychoses are separately discussed; and it is in this part of the book that problems of prognosis come to the fore. Prognostic aspects of psychiatry tend to be treated in a most cursory way in most Anglo-American textbooks. They are here given the attention that is due to their importance. Throughout, the reader will find a sane and balanced attitude to ætiology and psychopathology, and to the limitations of the various methods of treatment. If a criticism must be made, it is that the data provided about leucotomy are inadequate, both in the clinical and anatomical aspects, and that its use in other than schizophrenic psychoses is hardly considered.

Man's Quest for Significance. By Lewis Way. 1948. London. George Allen and Unwin. Pp. 211. Price 12*s*. 6*d*.

This is a diagnosis of our times, based on Adlerian psychology but without an unpleasant amount of psychological jargon. The argument runs as follows. In pre-industrial society every man had his own place, which provided him with a feeling of individual worth; with the advent of industrialization this was lost, and the individual became but one of a crowd, without social integration. Hence the popular demand for security. A similar anarchic change has taken place in the mutual relations of the sexes; the family is disorganized; children lack a stable background. Despite their gregariousness, all men are enemies of one another. Society, assuming greater responsibilities, stifles individual initiative. The environment is morally mediocre and physically sordid. Art and culture have nothing to say to the ordinary man. The populace is standardized at a dead level; and the omnipotent state introduces order only by trampling down private rights and individual opinions. The egoism of the majority glorifies itself in the worship of the community. Democracy declines. Political parties become reactionary or revolutionary, and ever more extremist. The extremist attitude spreads from the smallest to the largest units. Even the smaller nations are suppressed and regimented under the domination of one or two world powers. A re-orientation is imperative. The author suggests that the aim of any government should be to cultivate the worth of the individual. Although bureaucrats are happiest when persons can be treated as ciphers, the individual is the source of all values, the creator of every achievement, the moving force of history.

Probably, although almost every step in the author's thesis is disputable, and his presentation strikes the critical reader as partial and one-sided, his final conclusions will meet with general sympathy.

Du Réflexe au Psychique : Présentation du Système Nerveux. By Paul Cossa. 1948. 86 figs. Desclée de Brouwer, Bruges. Pp. 286. Price 125 fr.

This book is one number of a library, the Études Carmélitaines, which bears the imprint "L'attitude spiritualiste n'est ni plus gratuite ni plus irrationnelle que l'attitude mécaniste." It is therefore a work of science which has received the stamp of Catholic approval. As one might gather from the title it is a simplified but on the whole very full presentation of the present state of our knowledge of the anatomy and physiology of the human nervous system. It is intended for a non-medical as well as a medical audience. The first chapter is entitled "From Amoeba to Man"; but it is noteworthy that the comparative anatomy of the nervous system is only touched on, and there is no discussion of the theory of evolution. The rest of the book proceeds in an orderly manner from the simple reflex arc to higher nervous activity and finally to the physiology of perception, the clinical effects of neurological lesions, psychiatry, and a highly compressed account of psychoanalytic theory. It is made clear that investigations from the medical side account fairly satisfactorily for human behaviour in its physiological and more mechanistic aspects, but that the spiritual aspects of man are left as unexplained as heretofore. A final chapter by Père Philippe de la Trinité indicates the Catholic solution of the problems that medicine is unable to touch.

"Atlas of Peripheral Nerve Injuries." By W. R. Lyons and B. Woodhall. 1949. London and Philadelphia. W. B. Saunders Company. Pp. 339. Price 80*s*.

As a result of experience gained during the war the literature concerning peripheral nerve injuries has been, and will yet be, enhanced by several books published in this country and in the U.S.A. Few if any of these will be more lavishly produced than this atlas. The authors obtained their material from patients treated in two large American army hospitals that dealt with cases of peripheral nerve injury. In over three hundred beautiful plates, several in colour, they demonstrate the gross and macroscopic pathology of every type of traumatic nerve lesion. Each figure, and there are five or six figures to each plate, has an excellent and detailed legend, and in some cases a short clinical résumé and concluding comment are also provided. In this respect the title of the book is perhaps not sufficiently descriptive; it is essentially a pathological atlas, and although there are a few illustrations depicting limbs with injured peripheral nerves, anyone who is looking for guidance regarding the clinical effects of nerve injury will consult the book in vain. The text is of secondary importance to the photographs, but is nevertheless well written. The sections on traction lesions, associated nerve and vascular lesions, disrupted suture sites, and nerve grafts

are particularly interesting. American experience supports the view held by many in this country that the results of immediate nerve suture are almost invariably poor. Similarly the descriptions of the state of unsuccessful nerve grafts that were removed after a suitable interval for clinical recovery had elapsed are no more encouraging than those which have been published on this side of the Atlantic. The atlas will not have a wide appeal, but those interested in peripheral nerve injuries and especially neuropathologists will find it a source of much useful information. It should also be of great help to the general pathologist who is occasionally called upon to deal with material from nerve injury cases. The authors are commendably dogmatic regarding what they consider to be good and bad features from the point of view of prognosis in apposed nerve faces and resected segments. An extensive and accurate bibliography adds to the value of the atlas as a work of reference.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

The Sherrington Lectures. I : "Sensory Integration." By E. D. Adrian. 1949. University Press of Liverpool. Pp. 20. Price 1*s.*

Functional Localization in the Frontal Lobes and Cerebellum. By John F. Fulton. 1949. Oxford : The Clarendon Press. London : Geoffrey Cumberlege. Pp. xiii+140. Price 15*s.*

Acute Injuries of the Head. By G. F. Rowbotham. With a foreword by Prof. Norman M. Dott.

Rehabilitation of the Handicapped. Edited by W. H. Sodden, with a foreword by S. Licht. New York : Ronald Press Co. Pp. xiii+399. Price $5.00.

Transactions of the Ophthalmological Society of the United Kingdom. Vol. LXVII, Session 1947. 1948. London : J. and A. Churchill. Pp. lx+530, illustrated. No price given.

Brain and Behaviour. N. E. Ischlondsky. 1949. London : Henry Kimpton. Pp. xv+182. Price 21*s.*

Case Studies in the Psychopathology of Crime. B. Karpman. 1948. Washington : Medical Science Press. Vol. III, pp. xxxv+834. Vol. IV, pp. xxxv+875.

Psychological Aspects of Clinical Medicine. By Stephen Barton Hall. 1949. London : H. K. Lewis. Pp. xi+416. Price 21*s.*

The Mental and Physical Effects of Pain. By V. C. Medvei. 1949. Edinburgh : E. and S. Livingstone. Pp. 59. Price 3*s.*

A Miniature Textbook of Feeblemindedness. By Leo Kanner. 1949. New York : Child Care Publications. Pp. 33. Price $1.25.

The Mental Life of the Child. By Gustav Hans Graber. 1949. London : Staples Press. Pp. 158. Price 8*s.* 6*d.*

Modern Discoveries in Medical Psychology. Second edit. By Clifford Allen. 1949. London : Macmillan. Pp. xi+140. Price 15*s.*

Psychological Statistics. By Quinn McNemar. 1949. New York : John Wiley. London : Chapman and Hall. Pp. 364. Price $4.50. or 27*s.*

Psychosomatic Medicine. Second edit. By Edward Weiss and O. Spurgeon English. 1949. Philadelphia and London : W. B. Saunders Co. Pp. xxx+803. Price 47*s.* 6*d.*

A Psychiatrist looks at Tuberculosis. By Eric Wittkower. 1949. London : National Association for the Prevention of Tuberculosis. Pp. 152. Price 12*s.* 6*d.*

Masochism in Modern Man. By Theodor Reik. Trans. by Margaret H. Beigel and Gertrud M. Kurth. 1949. New York : Farrar, Straus. Pp. vi+439. Price $6.00 or 25*s.*

Human Personality and its Minor Disorders. By W. Harrowes. 1949 : E. and S. Livingstone. Pp. 260. Price 15*s.*

Über Zwischenhirnsyndrome. By F. Laubenthal. 1949. Stuttgart : Georg Thieme Verlag. Pp. 52. Price DM.3.60.

Die Insulin Lipodystrophie. By Ferdinand Adalbert Kehrer. 1949. Stuttgart : Georg Thieme Verlag. Pp. 50. Price DM.4.50.

Der Arzt der Persönlichkeit. By Ernst Speer. 1949. Stuttgart : Georg Thieme Verlag. Pp. 290. Price DM.26.00.

Medizin in Bewegung : Klinische Erkenntnisse und ärztliche Aufgabe. By Richard Siebeck. 1949. Stuttgart : Georg Thieme Verlag. Pp. xx+520. Price DM.27.00.

Klinische Psychologie. Second edit. By W. Hellpach. With supplements : " Klinische Psychologie des Kindesalters " by B. de Rudder, and " Klinische Möglichkeiten experimentelles Psychodiagnostik " by W. Witte. 1949. Stuttgart : Georg Thieme Verlag. Pp. viii+224. Price DM. 16.50.

Untersuchungen über den Lumbalen und Cervikalen Wirbelbandscheiben=vorfall. By F. Reischauer. 1949. Stuttgart : Georg Thieme Verlag. Pp. 87. Price DM. 9.60.

Leitfaden der Neurologie und Psychiatrie. By Wolfram Kurth. 1949. Stuttgart : Georg Thieme Verlag. Pp. xvi+305. Price DM. 22.00.

Lehrbuch der Psychiatrie. Eighth edit. By Eugen Bleuler. Revised by Manfred Bleuler in collaboration with others. 1949. Berlin : Springer-Verlag. Pp. x+506. Price DM. 26.00. Linen-bound, DM. 29.60.

Einführung in die Neurologie. By Oskar Gagel. 1949. Berlin : Springer-Verlag. Pp. vii+391. Price DM. 30.60.

Psychotherapeutische Studien. By Ernst Kretschmer. 1949. Stuttgart : Georg Thieme Verlag. Pp. 215. Price DM. 13.50.

Ein Querschnitt durch die Arbeit der Tübinger Nerven Klinik. Presentation volume to Ernst Kretschmer, by his pupils and collaborators. 1949. Berlin : Springer-Verlag. Pp. 420. Price DM. 36.00.

Von der Angst der Kranken. By Karl Scheele. 1949. Stuttgart : Georg Thieme Verlag. Pp. 76. Price DM. 4.80.

La Cataplessoterapia dell'Acceso di Tachicardia Parossistica. By Onofrio Giovenco. 1949. Genova-Nervi : Stab. Grafico Carto tecnico. Pp. 22. Price L.150.

Précis d'Anatomo-Physiologie Normale et Pathologique du Système Nerveux Central. Published under the patronage of Jean Lhermitte by Pieire Masquin and J. O. Trelles. Third edit. Paris : G. Doin et Cie. Pp. 494. Price 2.500 fr.

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Owing to the steadily increasing cost of production, it has been found necessary to raise the price of the *Journal of Neurology Neurosurgery and Psychiatry*, beginning with the first issue of 1950. The yearly subscription will then be 30s. (U.S.A. $5). Single copies remain at 7s. 6d. each.

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